Association between Vitamin D Status and Health Deterioration among First Generation Immigrants

Said Yousef Abdelrazeq

Thesis submitted to the University of Ottawa

in partial fulfillment of the requirements for the

Doctorate of Philosophy Degree

School of Epidemiology and Public Health

Faculty of Medicine, University of Ottawa

ABSTRACT

The increased number of international immigrants and associated global problems of health deterioration and vitamin D (vitD) deficiency/insufficiency may lead to significant burdens for host countries. This thesis investigated immigrants' health deterioration and vitD status through a comprehensive analysis of Canadian national vitD data, systematic evaluation of the quality/content of clinical practice guidelines, and global systematic review of vitD status and determinants among first-generation immigrants.

Immigrants had lower serum 25-hydroxyvitamin D (S-25(OH)D) and higher melanin levels than non-immigrants. S-25(OH)D levels improved over time, with ethnicity the main factor explaining variations. The longer immigrants lived in Canada, the higher the prevalence of chronic diseases (CDs), potentially reflecting health deterioration. Low levels of accumulated S-25(OH)D may impact CD-related biomarkers, partially explaining immigrants' health deterioration over time. Local and international guidance regarding immigrants' vitD deficiency/insufficiency was lacking.

Improving immigrants' vitD status requires prevention and intervention programs (e.g., vitD supplementation/screening), relevant national/international guidelines, and longitudinal research clarifying the complex bidirectional association between S-25(OH)D and CDs.

EXECUTIVE SUMMARY

Worldwide, immigrants experience deterioration in their physical and mental health after they arrive in their host country, with these changes often occurring within 5–10 years. Immigration studies suggest that the migration experience and post-migration integration may explain this decline in immigrants' health status. The integration process is likely to be a new experience for immigrants, and changes in their environments and lifestyles are well-documented factors that predispose migrants to chronic diseases (CDs). However, mechanisms underlying the decline in immigrants' health have not been explicitly identified.

International research evidence suggests that migration is a significant risk factor for low vitD levels attributable to resettlement-related changes in lifestyle. However, the ability of the body to create and maintain sufficient levels of vitD is also affected by socio-demographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and latitude), cultural and religious factors (e.g., clothing, sedentary behaviors, and prolonged breastfeeding time), lifestyle and dietary factors (e.g., vegetarian diet), and genetic and health factors (e.g., skin pigmentation and obesity). Immigrants have lower S-25(OH)D levels compared with the native-born populations of their host countries, although there are variations in vitD levels among immigrants based on sex, age, ethnicity, country of birth, skin pigmentation, nutritional factors, cultural practices, length of stay in the host country, and immigration class (e.g., refugees). Refugees are considered at particularly high risk for vitD deficiency.

The rapid growth in the number of international immigrants and the global problems of vitD deficiency and health deterioration among immigrants over time are expected to lead to significant burdens for the health systems of host countries. In addition to the absence of clear

strategies to prevent or delay the development of health deterioration, there is a lack of guidance to acknowledge the growing problem of vitD deficiency among immigrants at local and international levels. Therefore, this thesis aimed to investigate immigrants' health deterioration in the context of vitD status. The primary research question was, "Do the accumulated lower levels of vitD among immigrants explain their health deterioration after immigration?"

This thesis comprises three major studies (presented in Chapters 3–5) that were conducted to bridge identified knowledge gaps and support policymaking and program development at national and international levels. Each chapter presents one study and at least two associated manuscripts. The objectives as well as an overview of the methods and findings for these studies are summarized as follows.

Study (1): Analysis of Canadian Health Measures Survey (CHMS) data on vitamin D and first-generation immigrants

This study investigated the prevalence of and explanatory factors for vitD deficiency/insufficiency among first-generation immigrants compared with native-born Canadians. Moreover, the possible association between S-25(OH)D and chronic diseases and related biomarkers were examined as a proxy indicator for health deterioration. This study had three published manuscripts, all of which were based on analyses of CHMS data cycles three (2012–2013) and four (2014–2015). The study was designed to answer the following research questions. What are the explanatory determinants of vitD deficiency/insufficiency among first-generation immigrants in Canada? Do all immigrants have the same risk for vitD deficiency? Do melanin levels vary among immigrants based on ethnicity and country of origin? Do

melanin levels explain S-25(OH)D variations between immigrants and native-born Canadians? Are there any associations between S-25(OH)D levels and CDs? Are there any associations between S-25(OH)D levels and CD-related biomarkers?

The CHMS used a cross-sectional design and represented the total Canadian population, including immigrants from 153 countries and more than 13 ethnicities. The CHMS data contained unique health information and direct physical/blood measures, including S-25(OH)D and all vitD-related factors, such as sun exposure and skin pigmentation (melanin levels). Most importantly, health status and deterioration indicators in the CHMS were the prevalence of CDs diagnosed by healthcare professionals, self-reported general and mental health, and CD-related biomarkers.

Compared with non-immigrants, immigrants had lower S-25(OH)D levels. Younger and more recent immigrants were at higher risk for vitD deficiency/insufficiency. The longer immigrants had lived in Canada, the better their S-25(OH)D levels. Ethnic variations, dietary intake, melanin, and other lifestyle factors were the main predictors of/explanatory factors for lower S-25(OH)D levels among Canadian immigrants. Immigrants had higher melanin levels compared with non-immigrants. The study found a weak positive correlation between melanin and S-25(OH)D levels, and no difference by length of stay in Canada. The analysis highlighted that immigrants tended to have better health than non-immigrants in terms of the prevalence of CDs. In contrast, CD-related biomarkers and S-25(OH)D differed in favor of non-immigrants. Our findings suggested that the cumulative impact of lower S-25(OH)D among immigrants over time, changing biomarkers, and environmental and lifestyle changes after immigration may play crucial roles in subsequent health deterioration among immigrants.

Study (2): Chapter 4: Quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants' health

This systematic review aimed to collate and critically appraise CPGs relevant to immigrants' health and vitD. Moreover, the study evaluated whether the CPGs for vitD included recommendations for immigrants and clarified whether the CPGs for immigrants' health had recommendations on vitD. This study had three parts and two associated manuscripts. These were the protocol registration in PROSPERO (registered), protocol publication (published), and the full systematic review (submitted for publication). This systematic review was designed to answer the following research questions. Are current CPGs acknowledging the growing problem of vitD deficiency among immigrants? Are these CPGs following the development criteria for guidelines?

The protocol for this systematic review was registered with PROSPERO and then published. The study followed Cochrane methodology to systematically search the most recent CPGs across various electronic databases and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide preparation of the report. We used the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II) tool to evaluate the quality of the included guidelines. Overall, we identified 21 CPGs; 19 focused on vitD, and two that covered immigrants' health.

Around one-quarter of the included CPGs were rated as high quality. Recommendations regarding vitD were insufficient to address the growing problem of vitD deficiency among immigrant populations. National and international CPGs addressing vitD

deficiency/insufficiency among immigrants are needed to bridge the gaps between research, policy, and practice.

Study (3): Chapter 5: Global vitamin D status among immigrants

This study aimed to investigate the global status of vitD among immigrants to shed light on the growing problem of vitD deficiency. We systematically compared immigrants with non-immigrants, and also compared immigrants based on ethnicity, region, and country of birth. Furthermore, we presented findings in a systematic review and meta-analysis format. Following the World Health Organization (WHO) recommendation of monitoring and mapping the immigrant data, the results of vitD levels among immigrants compared with non-immigrants were mapped on different global maps. The focus of this systematic review was to include studies involving first-generation immigrants only and exclude studies with aggregated generations of immigrants.

This systematic review had three parts and is associated with five manuscripts. These are protocol registration in PROSPERO (registered), protocol publication (published), and the full systematic review with three planned manuscripts (in preparation). This systematic review was designed to answer the following research questions. What is the global status of vitD among first-generation immigrants compared with the native-born population of the host country? Do the same immigrants in a host country (e.g., Syrians in Canada) have the same S-25(OH)D levels in another host country (e.g., Syrians in Germany)? What are the key global factors for deficient or insufficient S-25(OH)D levels?

The design of this systematic review and meta-analysis followed the methods set out in the Cochrane Handbook for Systematic Reviews. The primary search strategy was completed in MEDLINE(R) ALL (Ovid) and translated to other databases to identify studies on vitD and immigrants. Distiller-SR was used for data screening and extraction, ArcGIS was used to create vitD maps, and RevMan to conduct the meta-analyses. The search strategy was developed and implemented on August 16, 2018, and updated in 2020. Moreover, the protocol for this systematic review was registered in PROSPERO in 2018 and published in 2019. The included studies were selected, and data were abstracted. This chapter provides a summary of the initial findings and sample global maps for S-25(OH)D levels for immigrants in different regions. The literature search will be updated and on which the final results will be based.

Conclusion

Immigrants had lower mean S-25(OH)D than non-immigrants (51.23 vs. 62.72 nmol/L, $p < 0.001$), and there were variations based on ethnicity and region or country of birth. Compared with native-born Canadians, the highest mean S-25(OH)D levels were found among immigrants born in the Netherlands, the UK, and Germany. In contrast, the lowest mean levels were found in Algeria, Lebanon, and Morocco. Ethnicity was the factor most strongly associated with S-25(OH)D, with the lowest mean levels reported for Japanese, Arabs, and Southeast Asians compared with the white grouping. Those with younger age at the time of immigration (<18 years) had a high risk for low vitD, and S-25(OH)D levels increased with the length of time they had lived in Canada. In addition, ethnicity, dietary intake, lifestyle, environmental, and biological factors such as skin pigmentation (melanin) remained the main predictors of/explanatory factors for vitD status among immigrants compared with native-born Canadians.

Skin melanin levels are associated with sociodemographic and behavioral characteristics. Although immigrants had higher melanin levels, these did not differ by length of stay in Canada. A weak positive correlation was found between melanin and S-25(OH)D, a finding that challenges existing knowledge and suggests there are different confounding factors that may interfere with such an underdeveloped relationship.

This research confirmed the healthy Canadian-immigrants' effect (advantage). Moreover, over time, immigrants experience more CDs than their non-immigrant counterparts. However, lower levels of accumulated S-25(OH)D among immigrants may impact their health profile in terms of CD-related biomarkers, partially explaining their health deterioration over time. Although vitD deficiency among immigrants has been detected globally for over five decades, our research showed that available guidance for vitD and immigrants' health was country-specific, and most guidelines should not be classified as CPGs. In addition to their low quality, the available guidelines did not adequately acknowledge the growing problem of vitD deficiency among immigrants. Our findings supported recommendations to bridge the knowledge gaps between research and practice concerning vitD and immigrants' health and may inform policy and program development at national and international levels.

THESIS…IDEA

Hope…Dream…Memory

My **hope** was to immigrate to Canada. For a period of **7 years**, I put a lot of effort into getting my papers accepted. My preparation included learning about immigrants' life in Canada and the difficulties that come with it. I was shocked to discover that, despite the lack of clear explanations, immigrants' health began declining a few years after settling in their new country.

Before moving to Canada, I achieved my **dream** of being admitted into the epidemiology Ph.D. program. As a topic for my thesis, along with my luggage, I chose to unpack the research question: "What are the factors and variables causing immigrants' health decline over time?" I had to wait another **7 years** to write this page because I had to overcome many obstacles, including the outbreak of the COVID-19 pandemic that prevented me from accessing my study data, which delayed my graduation.

The two journeys of moving countries and earning a graduate degree will create a new chapter in my **memory** that I will always cherish. The adventures and opportunities that the next **7 years** will offer remain to be seen. *Who knows*?

CONTRIBUTION OF THE AUTHORS

This thesis is based on six manuscripts discussed in Chapters 3, 4, and 5. Five were published, and one was submitted for publication. There are three more manuscripts in progress for Chapter 5, and two are planned based on the overall findings of this thesis.

All studies were designed in consultation and discussion with the thesis supervisor (Dr. George A. Wells), co-supervisor (Douglas Manuel) and advisory committee members (Drs. Ian Colman, Manny Papadimitropoulos, and Alomgir Hossain). All manuscripts were led by Said Yousef and co-authored by the thesis supervisor, co-supervisors, and the thesis advisory committee members. Yousef is the first and corresponding author in all thesis-related publications and was responsible for the data analysis and writing the manuscripts for all included studies.

Drs. Moez AlIslam Faris and Hayder A. Hasan were consulted on certain aspects and granted authorship in some publications. Lamia Hayawi, Maleka Ben Mahdi, Leenah Abdelrazeq, and Nazmun Nahar were part of the knowledge syntheses for the two the systematic reviews and granted authorship in some publications. Nathalie Leclair, Sarah Visintini, and Becky Skidmore are information specialists who contributed to peer-reviewing the search strategies for the two systematic reviews.

ACKNOWLEDGMENTS

Several people have supported me throughout my Ph.D. studies and significantly contributed to my success. I am deeply grateful to the following people for their encouragement and support throughout my years at the School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa.

I sincerely thank my supervisor, Dr. George A. Wells, for allowing me to pursue graduate studies at the University of Ottawa. George, I was grateful to pursue my degree under your leadership. Thank you for allowing me to chart my course throughout my Ph.D. program, providing me with guidance and constructive feedback, and giving me an immense amount of material, educational support, and time. Thank you for guiding me to stand and face the challenges of the COVID-19 pandemic. I am also grateful to my co-supervisor, Dr. Douglas Manuel, and advisory committee members, Dr. Ian Colman, Dr. Manny Papadimitropoulos, and Dr. Alomgir Hossain, for providing me with great insight, guidance and helpful feedback throughout my years as a doctoral candidate. I also appreciate Dr. Moez AlIslam Faris, who provided me with vitD-related educational materials. I further wish to express my gratitude to my colleagues (Lamia, Maleka, Nazmun), the information specialists, and COOLRDC staff for their support in the two systematic reviews and for facilitating access to the CHMS data.

I will remain in debt to my wife and loved children, Laith, Leenah, Abdulrahman, and Lojain, for their endless love, support, encouragement, and patience. I want to extend my deepest appreciation to my mom, brothers, sister, and friends. I share this accomplishment with all my family members.

Finally, your support and encouragement have meant the world to me. I would not have been able to have done this without you all; many thanks.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

A&HCI	Arts and Humanities Citation Index (1975–present)
AGREE-II	Appraisal of Guidelines, Research, and Evaluation-II
AHRQ	Healthcare Research and Quality
ArcGIS	Geographical information system
ATCs	Anatomical Therapeutic Chemicals
BMI	Body Mass Index
CAD	Canadian Dollar
CADTH	Canadian Agency For Drugs And Technologies In Health
CDs	Chronic Diseases (cardiovascular disease, cancer, chronic lung disease, and diabetes)
CHMS	Canadian Health Measures Survey
CI	Confidence interval
CIHI	Canadian Institute for Health Information
COOLRDC	Carleton, Ottawa, Outaouais Local Research Data Centre
CPAG	Canadian Physical Activity Guidelines
CPCIS	Conference Proceedings Citation Index - Science (1990–present)
CPCISSH	Conference Proceedings Citation Index-Social Science and Humanities (1990-resent)
CPGs	Clinical Practice Guidelines
DRIs	Dietary Reference Intakes
ESCI	Emerging Sources Citation Index (2005–present)
FST	Fitzpatrick skin type (I–VI)
GIN	Guidelines International Network
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
hs-CRP	high-sensitivity C-Reactive Protein
IAP	Indian Academy of Pediatrics
ICC	Intra-class Correlation Coefficient
IU/mL	International Units Per Milliliter
IgE	Immunoglobulin E
IOM	Institute of Medicine
JBI	Joanna Briggs Institute
kg/m2	Weight divided by height squared
MLIS	Medical Library Information Specialist
NICE	National Institute for Health Care Excellence
NIH	National Institutes of Health

nmol/L	Nanomoles per liter
NOS	National Osteoporosis Society
OR	Odds Ratio
PECO	Population, Exposure, Comparator, and Outcomes
PICO	Population, Intervention, Comparator, and Outcomes
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol
r	Correlation
REB	Research Ethics Board
RIMHS	Medical and Health Sciences
ROB	Risk of bias tool
ROBINS-E	Risk Of Bias In Non-randomized Studies of Exposure
ROS	Royal Osteoporosis Society
S-25(OH)D	Serum 25-hydroxyvitamin D (serum vitamin D)
S	Sets of summary statistics
SBEM	Brazilian Society of Endocrinology and Metabology
SCI-EXPANDED	Science Citation Index Expanded (1900– present)
SE	Standard Error
SIGN50	Scottish Intercollegiate Guidelines Network-Publication no. 50
SSCI	Social Sciences Citation Index (1900–present)
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TC/HDL ratio	Total Cholesterol/high-density Lipoprotein Cholesterol ratio
TRIP	Turning Research Into Practice
USPSTF	U.S. Preventive Services Task Force
UVB	Ultraviolet-B
VitD	Vitamin D
VitD2	Vitamin D2
VitD3	Vitamin D3
WHO	World Health Organization

Chapter 1: Introduction

1.1 Statement of the problem

Canada has the highest ratios of immigrants and refugees among the industrialized Western countries, with a very well-regulated immigration system. [1]. Immigrants' ethnocultural diversity contributes to Canada's unique population diversity [2]. Historically, before 1971, most Canadian immigrants (78.3%) came from Europe. In 2011, nearly 17.2% of the Canadian population were first-generation immigrants; the largest group came from Asia (57%). By 2016, the percentage of firstThe number has increased to 21.9% in 2016 [2, 3]. Recently, Statistics Canada estimated an increase of approximately 1 million foreign-born residents every 3 years by 2035/2036 and approximately 50% of the Canadian population will comprise immigrants and their Canadian-born children by 2041 [3, 4]. However, these changes in the past and coming few decades in patterns, volume, and demography are expected to cause significant burdens for the Canadian healthcare systems to carry out further changes in the existing health and immigration policy frameworks [1, 2, 5, 6].

Most of the international population movement is for seeking work, while violence, conflicts, natural disasters, and human rights abuses may force others to move out from their normal place of residency [7, 8]. Migration is an international act and often challenging. Changes in lifestyle and environment, language barriers, social isolation, inequity, and resettlement stress are some of these difficulties that are more prominent to immigrants [9, 10]. Research evidence suggests that these factors contribute to the global phenomena of decline of healthy immigrant effect after immigration, while the reasons not yet established [9, 11, 12]. Lower vitD levels among immigrants compared to native-born population of the host countries is an emerging global immigrants' health problem [10, 13-15]. Refugees, a subgroup of immigrants, non-

Western immigrants were identified to be at higher risk for vitD deficiency as compared to other immigrant population groups [10, 14-17]. Skin pigmentation and environmental factors including lifestyle changes were linked to the deficient/insufficient levels of vitD among immigrants [10, 18-21].

The focus of this thesis was on these two global immigrants' health problems with an overall objective of investigating immigrants' health deterioration in the context of vitD status to bridge the knowledge gaps and to supports policymaking and program development at national and international levels.

1.2 Objectives and research questions

This thesis comprises three major studies, namely: a secondary analysis of two Canadian Health Measures Survey (CHMS) cycles; a systematic appraisal of clinical practice guidelines (CPGs); and a systematic review and meta-analysis for global vitD among immigrants. The overall objective was to investigate the status of vitD and its association with health deterioration among first-generation immigrants. The overall thesis research question is

"Dose the accumulated lower levels of vitD among immigrants explain the health deterioration after immigration?"

The following are three major objectives to address the thesis research questions:

Objective 1: To investigate the prevalence and determinants of vitD deficiency/insufficiency among first-generation immigrants compared with native-born Canadians. Also, to identify explanatory covariables for variations in vitD levels between immigrants from different ethnicities and origins compared to non-immigrants. Moreover, to investigate immigrants' health status and possible health deterioration in relation to S-25(OH)D levels.

This study was designed to answer the following research questions: What are the levels of S-25(OH)D among first-generation immigrants in Canada compared to the native-born population? Are S-25(OH)D levels among first-generation immigrants in Canada vary based on ethnicity, country of birth or region? What are the explanatory determinants of vitD deficiency/insufficiency among first-generation immigrants in Canada? Do all immigrants have the same risk for vitD deficiency? Do melanin levels vary among immigrants based on ethnicity and country of origin? Do melanin levels explain S-25(OH)D variations between immigrants and native-born Canadians? Are there any associations between S-25(OH)D levels and CDs? Are there any associations between S-25(OH)D levels and CD-related biomarkers?

Objective 2: To systematically and critically appraise the CPGs that are relevant to immigrants' health and CPGs relevant to vitD. Moreover, to evaluate whether the CPGs of vitD including recommendations for immigrants and clarify whether the CPGs of immigrants include recommendations on vitD.

This study was designed to answer the following research questions: Do the available vitD's CPGs and immigrant health's CPGs comply with the quality development standards? Do immigrant CPGs include recommendations on vitD? Do vitD CPGs include recommendations for immigrants, including refugees and asylum seekers?

Objective 3: To shed some light on the growing pandemic of global vitD deficiency among immigrants by systematically compareing the global vitD status of immigrants to non-immigrants and between immigrants based on ethnicity, region, and country of birth. Furthermore, to present details in a systematic review and meta-analysis format and to illustrate vitD levels in different global maps.

This study was designed to answer the following research questions: What is the global status of S-25(OH)D among first-generation immigrants compared to the native-born of the host country? Are S-25(OH)D levels different between the same ethnic groups of first-generation immigrants in different regions worldwide? What are the key factors for vitD deficiency/insufficiency among first-generation immigrants?

The following section will describe in detail the objectives and hypotheses associated with each section of this dissertation.

1.3 Chapter outlines

This thesis consists of six chapters, a general overview of each chapter and their sections are described as follows:

Chapter 1. Introduction:

This introductory chapter presents an overall introduction and focuses on the objectives and the rationale for the thesis.

Chapter 2. Background:

This chapter provides an epidemiological background on national and international immigrants, as well as scientific and the epidemiological background on vitD.

Chapter 2 provides general background information relevant to the three main chapters of this thesis (Chapters 3, 4, and 5). This information includes epidemiological background on national and international immigrants, immigrants' health, and vitD. Moreover, the chapter contains scientific and epidemiological background on vitD. This includes a fundamental insight into vitD's synthesis, function, absorption, metabolism, adequacy, safety, toxicity, and the methods of measuring S-25(OH)D in the blood. The chapter also covers the global status

and determinants of S-25(OH)D, the risk of skeletal and non-skeletal health diseases due to lower levels of S-25(OH)D, and the Clinical practice guidelines (CPGs) relevant to vitD and to immigrants' health. The Chapter also provides an overview of the national Canadian data (CHMS) on vitD and immigrants that were used in the analysis of Chapter 3. Moreover, we conclude this Chapter with the thesis rationale and a short summary.

Chapters 3. Analysis of national data (CHMS) on vitamin D and first-generation immigrants:

This chapter presents a comprehensive analysis of national Canadian data on vitD and immigrants and has three sections (Sections 3.1–3.3), each represent a manuscript. The title and publication status of the three manuscripts three are as follows:

> **Section 3.1:** Vitamin D Status among First-generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey (*Published*)
>
> **Section 3.2:** Melanin levels in relation to vitamin D among first-generation immigrants from different ethnic groups and origins: A comparative national Canadian cross-sectional study (*Published- in press)*
>
> **Section 3.3:** Vitamin D and Chronic Diseases among First-generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data (*Published*)

Chapter 4. Quality and content of clinical practice guidelines for vitamin D and for immigrants:

This chapter provides systematic critical appraisal for the quality and contents of CPGs pertaining to vitD and immigrants and has two sections (Sections 4.1and 4.2). The publication status and title of the two manuscripts are as follows:

Section 4.1: Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: a protocol for systematic review. *This protocol was registered with PROSPERO (CRD42021240562) in 2021 and published in 2022.*

Section 4.2: Assessment of the quality and content of clinical practice guidelines for vitamin D and for immigrants using the AGREE II instrument: A systematic review (*submitted for publication*)

Chapter 5. Global status of vitamin D among immigrants:

This chapter evaluates the global status of vitD among immigrants compared to non-immigrants and has two major sections (Sections 5.1 - 5.2). Section 5.2 has three manuscripts. The publication status and title of the four manuscripts are as follows:

Section 5.1: Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations: A systematic review and meta-analysis. *This protocol was registered with PROSPERO (CRD42018086729) in 2018 and published in 2019.*)

Section 5.2.1: Global vitamin D Status among first-generation immigrants from different ethnic groups and origins compared to native-born population (*Initial results- in progress*)

Section 5.2.2: Mapping global vitamin D status among first-generation immigrants from different origins compared to native-born population (*Initial results- in progress*)

Section 5.2.3: Global determinants for vitamin D deficiency/insufficiency and variations among first-generation immigrants (*In progress*)

Chapter 6. Discussion and Conclusion:

This is a summary chapter incorporates the major findings and highlights thesis strengths, limitations, recommendations, and future work and research directions.

References

1. Council on Foreign Relations. *What Is Canada's Immigration Policy?* 2022 February 9, 2022; Available from: https://www.cfr.org/backgrounder/what-canadas-immigration-policy.
2. Statistics Canada, *Immigration and Ethnocultural Diversity in Canada. National Household Survey, 2011.* Statistics Canada, 2013. **Catalogue no. 99-010-X2011001**(99): p. 23-23.
3. Statistics Canada. *Canada in 2041: A larger, more diverse population with greater differences between regions*. 2022; Available from: https://www150.statcan.gc.ca/n1/en/daily-quotidien/220908/dq220908a-eng.pdf?st=K13tiyuc.
4. Statistics Canada. *Population Projections for Canada, provinces and Territories*. 2014 [cited 2021 20/11/2021]; Available from: https://www150.statcan.gc.ca/n1/en/pub/91-520-x/91-520-x2010001-eng.pdf?st=LWFifucU.
5. Gushulak, B.D. and L.S. Williams, *National Immigration Health Policy Existing Policy, Changing Needs, and Future Directions.* CANADIAN JOURNAL OF PUBLIC HEALTH, 2004. **95**(3): p. 1-27.
6. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.
7. WHO, *Report on the health of refugees and migrants in the WHO European region: no public health without refugee and migrant health.* 2018.
8. WHO. *Refugee and migrant health*. 2022 May 2022 [cited 2022 Oct. 2022]; Available from: https://www.who.int/news-room/fact-sheets/detail/refugee-and-migrant-health.
9. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
10. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.
11. Sanou, D., et al., *Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.
12. Vang, Z., et al., *The Healthy Immigrant Effect in Canada: A Systematic Review.* Population Change and Lifecourse Strategic Knowledge Cluster Discussion Paper Series/Un Réseau stratégique de connaissances Changements de population et parcours de vie Document de travail 2015. **3**(1): p. 4.
13. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

14. Eggemoen, Å.R., et al., *Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults.* BMJ open, 2013.

15. Aucoin, M., et al., *Vitamin D status of refugees arriving in Canada Findings from the Calgary Refugee Health Program.* 2013. **59**.

16. Baauw, A., et al., *Health needs of refugee children identified on arrival in reception countries: A systematic review and meta-Analysis*, in *BMJ Paediatrics Open*. 2019, BMJ Publishing Group.

17. Lips, P., et al., *Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society.* European journal of endocrinology, 2019. **180**(4): p. P23-P54.

18. Centers for Disease Control Prevention. *Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination.* . 2013; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf.

19. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

20. Gaksch, M., et al., *Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium.* PLOS ONE, 2017. **12**(2): p. e0170791-e0170791.

21. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide*. British Journal of Nutrition, 2014. **111**: p. 23-45.

Chapter 2: Background

Chapter overview

This chapter provides epidemiological and scientific background information about immigrants and their health deterioration at national and global levels and offers basic scientific knowledge on vitD levels and vitD deficiency among immigrants. Moreover, it presents an overview of Canadian national data on vitD, followed by a summary and a rationale for this thesis.

2.1 Immigrants

2.1.1 Migration and immigrants' health

Most of the international population movement is for seeking work. Violence, conflicts, natural disasters, and human rights abuses may force others to move from their original country of residence [1, 2]. Approximately 281 million (one in every 30 people) are international migrants, 84 million people are forced to leave their homes, 26.5 million are refugees, and 4.4 million are asylum seekers [1, 2]. Migration is an international phenomenon and often challenging [1]. Some of these difficulties include changes in lifestyle and environment, language barriers, social isolation, inequity, and relocation stress [3]. Although immigrants become a vital part of the host countries over time, the integration process has an impact on immigrants' health as well as on the whole system of the host countries [1].

Canada has the highest ratio of immigrants and refugees among the industrialized Western countries, with a very well-regulated immigration system. [4]. Immigrants' ethnocultural diversity contributes to Canada's unique population diversity [5]. Historically, before 1971, most Canadian immigrants (78.3%) came from Europe. In 2011, nearly 17.2% of the Canadian

population were first-generation immigrants, including the largest group (57%) who came from Asia. The percentage increased to 21.9% in 2016 with ethnocultural diversity of Canada's immigrant population with close to 200 countries as a place of birth and more than 200 ethnic origins. [5, 6]. Recently, Statistics Canada estimated an increase of approximately 1 million foreign-born residents every three years by 2035/2036. About 50% of the Canadian population will be comprised of immigrants and their Canadian-born children by 2041 [6, 7]. However, these changes in the patterns, volume, and demography during the past and coming few decades are expected to impact Canada's overall healthcare system and to lead to further changes in the existing health and immigration policy frameworks [4, 5, 8, 9].

A significant portion of immigrants is usually based on voluntary immigration choice who were restricted by immigration policies and regulations in the host countries. Despite particular groups such as refugees, immigrants appear to be healthier than non-immigrants [10-14].

The phenomenon of the "healthy immigrant effect" or "healthy immigrant advantage" indicated a health status where recent immigrants have better health than that of the residents in the host country, including long-term immigrants from previous migrations [11, 13, 14]. Studies show significant differences between first-generation and second or third-generation immigrants in terms of socio-cultural (e.g., socioeconomic status and cultural beliefs) and various health outcomes (e.g., depression, cancer, and diabetes) [15, 16]. In addition, the healthy immigrant effect varies between immigrants at the time of immigration and during resettlement in their new host country [14]. Previous immigrant health studies suggested that premigration factors, such as rigorous selection criteria that favour immigrants who are

healthier, wealthier, and better educated contribute to the healthy immigrant effect "advantage" [11, 14].

Health deterioration among immigrants is a global concern [1, 11, 17, 18]. Migration studies indicate that the integration process is likely a new experience for immigrants. In addition to pre-migration factors, post-migration, new environment, and lifestyle changes are well-documented factors predisposing migrants to chronic diseases [1, 12, 19].

The physical and mental health of immigrants often declines quickly following arrival in their host countries [11, 20, 21], and further health changes occur over the next 5–10 years [11, 13, 14, 22]. The underlying reasons for health deterioration have not been explicitly identified [11, 14].

"Health" is articulated as "the capacity of people to adapt to, respond to, or control life's challenges and changes" [23]. Likewise, both native-born and foreign-born populations are affected by medical, psychosocial, behavioral, and environmental determinants [24]. Challenging intergation factors associated with migration and post-migration, including changes in their psychosocial and environmental factors, are unique experience to immigrants. These factors were believed to explain the decline in the health status of immigrants after arrival to the host country [3, 11, 20, 24-27].

2.1.2 Immigrants' health and vitamin D

Globally, immigrants have lower S-25(OH)D levels compared with native-born populations [3, 28]. Research studies found that vitD status varies among immigrants based on their immigration status (voluntary immigrants, refugees, and asylum seekers). For instance, refugees have a higher risk for vitD deficiency than other immigrant population groups [3, 29-31]. The European Calcified Tissue Society also identified non-Western immigrants as a

specific group at higher risk for vitD deficiency that should receive vitD supplementation [32]. Skin pigmentation, clothing type, ethnicity, place/region of birth, length of time after immigration, changes in diet, physical activity, and sun exposure also contribute to vitD variations [3, 33-35]. In a systematic review (data from 112 articles, 44 countries, and 168,389 participants), a wide range of S-25(OH)D between 4.9 and 136.2 nmol/L was reported with age and sex variations. One-third of these studies reported mean levels below 50 nmol/l [36]. Epidemiological studies show vitD deficiency and or insufficiency were more common among subgroups of immigrants such as dark-skinned, Middle Eastern, and African populations, those who migrate from equatorial regions to the northern latitude, and those who dress in concealed clothing as part of their culture and lifestyle practices [3, 36, 37]. A meta-analysis of 36 studies estimated the prevalence of vitD deficiency among dark-skinned immigrants was 77% (95% CI 70%, 83%) that was attributable to the length of stay in the host country, age at immigration, nutritional barriers, and geographic origins and ethnicities [3].

Researchers recommended future studies to assess relevant data on vitD and determinants, including lifestyle factors; as well as, to compare subgroups of the population within the same country [36]. Moreover, it is important to study and compare ethnic groups from the same generation [15, 16, 38, 39]. Other studies suggest establishing links between vitD, immigration status, and disease status [19]**.**

2.2 Vitamin D

2.2.1 Sources, and synthesis (UV radiation) of vitamin D

Vitamin D comprises several fat-soluble secosteroids, prohormones, and metabolites [40]. VitD is crucial for calcium absorption and bone mineralization [41]. Sufficient levels of vitD can maintain calcium hemostasis as it enhances calcium absorption in the small intestines [40].

VitD plays a crucial role in physiological functions, including skeletal and non-skeletal health [42] and has two primary metabolites, namely 25-hydroxyvitamin D (25-OH) and 1, 25 dihydroxy vitamin D [43].

In addition to the natural sources of food-based and sunlight, the human body obtains vitD from artificial sources such as supplements and fortified food [44-46]. VitD is commonly known as the ‘sunshine vitamin” due to its primary source through skin exposure to ultraviolet B (UVB) (290–320 nm) radiation from sunlight (cutaneous synthesis of vitD3) [43, 45-47].

Because vitD cannot be naturally found in many foods, and the fortification of food with vitD is not consistent, it is assumed that worldwide sunshine is the primary resource of the vitamin. However, sunshine exposure is a variable quantity around the world and is affected by many factors such as seasons, latitudes, daytime, skin pigmentation, and the use of sunscreens. These factors significantly affect the degree of vitD generation by the human skin [28, 48]. Enough exposure to UVB light in the wavelength of 290–320 nm has massive benefits in synthesizing the vitD in the skin [48], while excessive exposure is a risk factor for sunburn and skin carcinogenesis [49]. Despite the year-round availability of sunshine in most countries, vitD insufficiency is common in several regions of the world [42]. People living in lower UVB radiation regions may have a biological adaptation process as part of micronutrient gene regulation over time that supports vitD3 synthesis [50]. Dark-skinned individuals have a rich amount of melanin, which may act as a biological shield against UV radiation [28]

The dietary sources for vitD are plant-based foods (vitD2 or ergocalciferol) and animal-based foods (vitD3 or cholecalciferol) [45, 51]. VitD2 and vitD3 are believed to have equal biological value [42]. Both mushrooms (grown in UV light) and fortified food are good sources of vitD2. Fatty fish (e.g., salmon, mackerel, and tuna fish) are considered a great

source of vitD3 [40, 52]. The pharmaceutical sources include prescriptions of vitD2 (e.g., Ergocalciferol and Drisdol) and over-the-counter supplements (e.g., multivitamins and vitD3) [42].

The total concentrations of 25(OH)D are the primary circulating form of vitD and represent the combined contributions of the cutaneous synthesis, supplementary, and dietary intake of vitD (vitD2 and vitD3). The 25(OH)D is considered the top clinical marker for overall serum or plasma 25(OH)D level [28, 45, 51, 53-55].

2.2.2 Function, absorption, and metabolism of vitamin D

The primary function of vitD is to help maintain calcium homeostasis [40], which serves a role in maintaining sufficient calcium and phosphorous levels in the human body to provide optimal metabolic functions [56]. Moreover, vitD is thought to have a role in maintaining muscle mass and function. For instance, vitD deficiency has been strongly associated with chronic musculoskeletal pain, muscle weakness, and an increased risk of falling [42, 57].

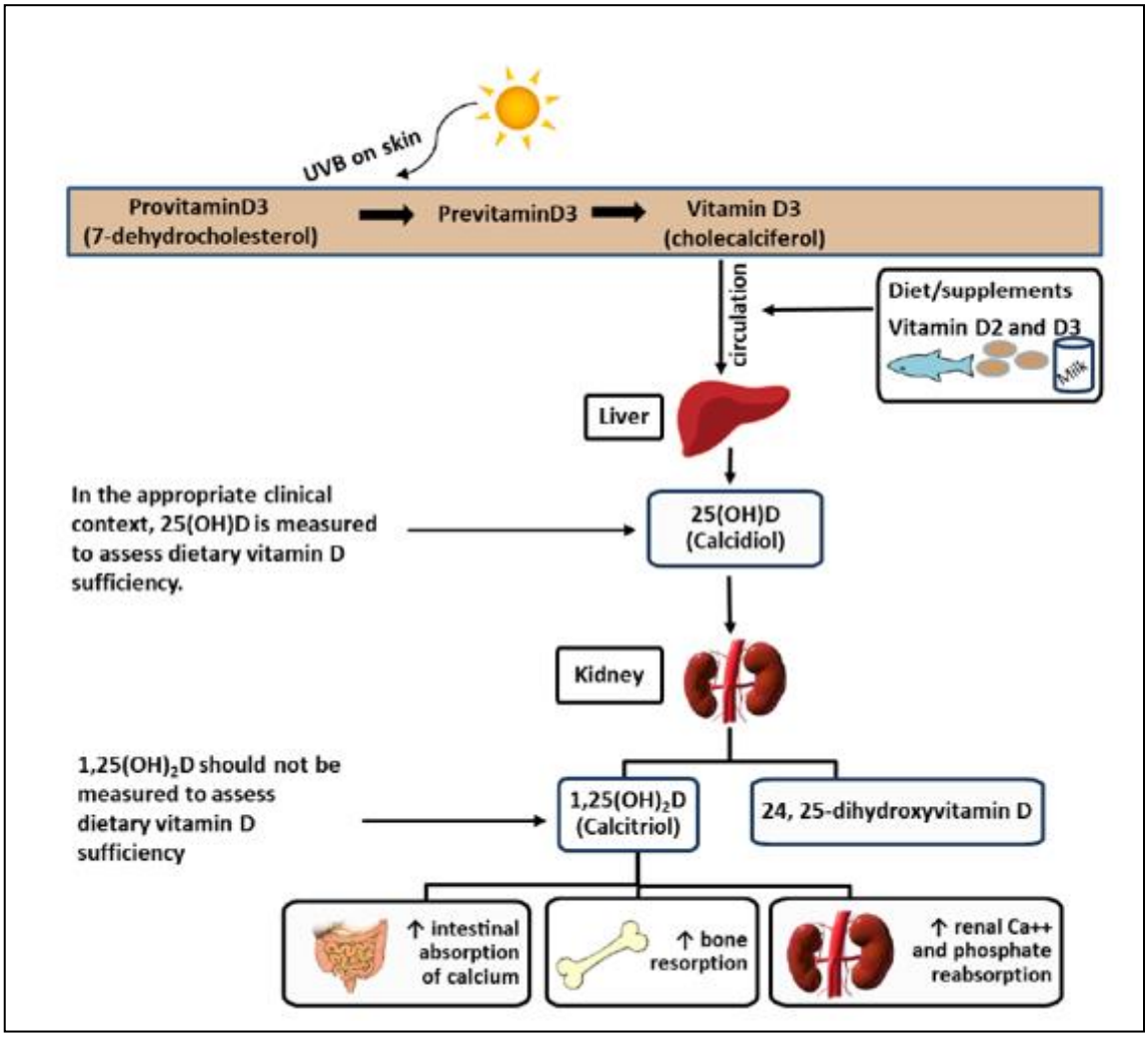
In addition to skin synthesis of vitD3, vitD2 and vitD3 are transported via the bloodstream to the liver [58]. Both are converted to 25(OH)D, which is considered the best biomarker for overall vitD [58, 59].

The 25(OH)D requires further hydroxylation in the kidneys to the biologically active form of 1,25(OH)2D, which is tightly regulated by the parathyroid hormones. The active state is considered not a valuable measure of vitD status due to its short half-life (15 hr) compared to the stable half-life (2-3 weeks) for the 25(OH)D [58-60].

Some factors influence vitD synthesis in the skin, including biological and environmental factors [61]. For instance, due to age-related declines of skin 7-dehydrocholesterol, vitD

synthesis is less effective in older people [42]. Melanin reflects the degree of skin pigmentation and inhibits cutaneous vitD3 synthesis because of its function as a biological shield against UV radiation [62]. The concentration of S-25(OH)D to skin melanin levels was controversially reported in previous studies [42, 49]. Studies show that people of darker skin (with higher skin melanin levels) have lower S-25(OH)D and need more UVB exposure. In contrast, other studies found no change in vitD synthesis regardless of differences in skin pigmentation [42, 49]. Figure 1 shows synthesis, circulation, and metabolism of vitD.

Fig.1. Synthesis and metabolism of vitamin D (Modified from the British Colombia Guideline) [58].



2.2.3 Adequacy, safety, and toxicity of vitamin D

The concentration of 25(OH)D represents the combined contributions of the cutaneous synthesis and the dietary intake of vitD. It is considered the most appropriate clinical indicator of overall vitD [37]. There is no international agreement regarding the reference range for the concentration levels of S-25(OH)D [63]. The mean of 25(OH)D and/or the ranges for the thresholds limits of deficiency (<25–30 nmol/L), insufficiency (25–49 nmol/L), and sufficiency (≥50–<75 nmol/L) were commonly reported, and used in studies to describe the vitD status [28]. The insufficient vitD status is more frequently used as of <50 nmol/L to describe hypovitaminosis D [61]. The deficient levels of S-25(OH)D were inconsistently defined by the World Health Organization as levels below 25 nmol/l and by the Institute of Medicine (IOM) as levels below < 30 nmol/L [64, 65].

The optimal 25(OH)D concentration levels are controversial. The IOM recommends maintaining 25(OH)D concentration levels above 50 nmol/L. In contrast, other experts either favour the concentration between 50 to 100 nmol/L or assert the need for more evidence to support safe limits [63, 64, 66].

The danger of toxicity for highly increased 25(OH)D levels must be considered when determining vitD status and needs. For instance, hypercalcemia and/or hypercalciuria are symptoms of vitD poisoning, which could be associated with reduced glomerular filtration rate, high calcium uptake in the intestine, and bone turnover [43]. However, toxicity due to vitD may arise by prolonged supplementation and not due to endogenous synthesis; and in very rare cases, it happens from fortified food [43].

Recent studies on the safety of vitD reported different 25(OH)D levels of toxicity or levels that need to be avoided [43]. For instance, over a limit of 125 nmol/L is indicative of

detrimental consequences of adverse effects, below 220 nmol/L offers no significant risk of harm [43], and levels of > 250 nmol/L among hospitalized patients were found in 4.1% of whom 2.7% had toxic >375 nmol/L level [67]. In a recent Cochrane review, hypervitaminosis (very high levels of S-25(OH)D) was reported in the included studies as > 225 nmol/L [68].

2.2.4 Methods of measuring S-25(OH)D in blood

The 25(OH)D has a stable half-life (up to three weeks) in the human body [53], and is expressed in nanogram per millilitre (ng/mL) or nanomoles per litre (nmol/L) in which 1ng/mL equal 2.496 nmol/L [42, 60, 64]. Several tests have been developed and utilized by different laboratories worldwide to either measure 25(OH)D2, 25(OH)D3, or a total of 25(OH)D [42, 69]. Measuring 25(OH)D3 only can give misleading results regarding the vitD status of the patient [42]. Diagnosing individuals and categorizing vitD status based on the levels of 25(OH)D depend on reliable and accurate laboratory measurement methods. These methods vary between laboratories in different countries [42, 69]. Immunoassays and chromatographic techniques are commonly used and are becoming the gold standard for measuring circulating vitD [42, 70]. Immunoassays can be classified into four main categories known Competitive Protein Binding Assay (CPBA), Radioimmunoassay (RIA), Enzyme-Linked Immunosorbent Assay (ELISA), and Chemiluminescent Immunoassay (CLIA) [71]. Each of these methods has its strengths and weaknesses. For instance, the advantages of CPBA are that it is inexpensive, detects and measures vitD2 and vitD3, and handles large and small sample sizes. However, its limitation is that it is affected by other insignificant and interfering metabolites of vitD, such as 24,25-dihydroxy vitamin D [72-74]. The RIA method is cost-effective, rapid, and employs radioactive elements for vitD metabolites detection, which can detect trace levels of vitD and vitD2 and vitD3. However, it can overestimate vitD levels because the sensitivity

of this test is not limited to D2 and D3 [51, 71, 72]. CLIA is a fully automated assay widely used in most clinical laboratories today. It is safer, faster, and less labour-intensive than other assays, such as the RIA technology [70, 72]. ELISA vitD tests implement labelled enzyme that changes colour upon the binding of an antibody-antigen complex and has a few techniques available such as direct ELISA, indirect ELISA, sandwich, and competitive. Direct is the easy and fast technique; however, using any of these techniques is also limited by their strengths and drawbacks [70, 71] [75].

The chromatographic use separation techniques split a mixture into its different constituents. HPLC, Liquid Chromatography Mass Spectroscopy (LC-MS), and LC-UV are the most common chromatographic techniques used for vitD testing. HPLC has a fast separation process with lower cost than the other chromatographic techniques. LC-MS has high separating power with the capability of measuring 25(OH)D2 and 25(OH)D3 with high sensitivity towards various concentrations. LC-UV is less specific and more sensitive to interfering substances than LC-MS. Disadvantages such as high cost and large sample size may favour the employment of one technique over the other [51, 70, 73, 74, 76, 77]. Chromatographic techniques are more reliable, precise, selective, and accurate than immunochemical techniques. However, immunoassay methods produce faster results than the chromatographic methods [78].

Intraassay and interlaboratory variability should be considered when measuring vitD using these different methods. Therefore, it was suggested that the threshold cut-points need to be method specific rather than universal [51, 70, 77]. In clinical practice, using an unreliable assay to measure S-25(OH)D may result in under or overestimating the total blood levels, misleading physicians, and vitD2 supplementation may be unnecessarily prescribed. For

instance, using a laboratory assay that measures only 25(OH)D3 could underestimate total levels of 25(OH)D [42].

2.3 Health consequences on vitamin D

2.3.1 Global status of S-25(OH)D levels

Over the past few years, vitD has become one of the most active clinical and epidemiological research topics. Despite the levels of sunlight, vitD deficiency has become a global health problem in all age groups and regions [28, 37, 79]. Consequently, in the past few decades, scientists have studied and gathered overwhelming evidence linking vitD deficiency to skeletal and non-skeletal health [42, 54]. Worldwide, an estimated 1 billion people have vitD deficiency or insufficiency (25(OH)D < 50 nmol/L) [42].

Several factors affect the human body's ability to create and maintain sufficient S-25(OH)D levels. Namely, these may fall under socio-demographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and latitude), cultural, behavioral, and religious factors (e.g., clothing, sedentary lifestyle, smoking, and prolonged breastfeeding time), lifestyle and dietary factors (e.g., vegetarian diet), as well as genetic and health-related factors (e.g., skin pigmentation and obesity) [3, 19, 37, 47, 80].

In a global review of evidence on vitD status and determinants of hypovitaminosis, the leading risk factors for vitD deficiency were older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, poor dietary habits, and absence of vitD fortification [61]. Moreover, skin pigmentation was reported in a systematic review as the most attributable factor for vitD status [3].

2.3.2 Low vitamin D status and risk of skeletal and non-skeletal health diseases

Vitamin D levels have been connected to skeletal and non-skeletal health [19, 54]. Previous studies linked chronic diseases as an indication of the health status of the population to lower levels of S-25(OH)D [79, 81-83].

Although there are arguments about optimal levels of S-25(OH)D, evidence suggests that levels below < 30 nmol/L are associated with an increased risk of chronic diseases. Whereas S-25(OH)D levels above 75 nmol/L were found to be the most health-advantageous levels for all age groups [54].

Vitamin D deficiency and inadequate dietary calcium intake (< 400-500 mg/day) are most common among children who have rickets or adults who have osteoporosis. Patients with vitD deficiency have poor absorption of dietary calcium and phosphorus in the small intestine, up to 15% and 60%, respectively. As a result of decreased ionized calcium, a compensatory mechanism may cause secondary hyperparathyroidism among vitD deficient patients [42].

Low levels of S-25(OH)D status were found to be related to bone deformations and to increasing the chance of falls and bone fractures [44, 54]. Moreover, lower or deficient levels of vitD have been linked to autoimmune disease such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and lupus [64], and weakness of skeletal muscles [84]. Moreover, vitD deficiency may mediate fracture risk due to higher susceptibility to falls [84]. However, a combination of vitD and calcium supplements was found to be more efficient for skeletal health to prevent fractures [85].

Researchers hypothesized that the inadequate or deficient level of vitD is associated with an increased risk of all-cause mortality and a wide range of physical and mental health diseases. These include osteoporosis, type 1 diabetes mellitus, cancer, cardiovascular disease, obesity,

schizophrenia and depression, and metabolic syndrome [19, 35, 36, 54, 86, 87]. VitD deficiency has also been linked to age-related neurodegenerative disorders such as dementia and Alzheimer's. VitD supplementations were found to play a role in slowing the progression of Parkinson's and Alzheimer's diseases [88, 89]. Higher levels of S-25(OH)D (e.g., in a range of 40-60 ng/ mL) were found to be associated with a lower risk of developing several types of cancer and a lower rate of cardio-metabolic disorders, including hypertension, dyslipidemia, type 2 diabetes and peripheral arterial disease [42].

In addition to the main function of vitD to maintain calcium and phosphate absorption, it is an immunoregulatory hormone. VitD has been proven in studies to have major physiologic effects on innate and adaptive immune responses [42]. Recent reviews regarding the effect of vitD on skeletal and extra-skeletal disease suggest that low S-25(OH)D is a marker rather than a cause of extra-skeletal illness, and this association may be mediated by inflammation [85].

Various immune cells, such as lymphocytes, monocytes, macrophages, and dendritic cells, express the vitD receptor and metabolizing enzymes in a biologically probable mechanism of conversion of circulating vitD2 and vitD3 to the active (calcitriol) form. This process will not occur with deficient or insufficient S-25(OH)D levels, which may lead to dysregulation of immune responses [90]. Moreover, recent publications supported the hypothesis that vitD deficiency was related to the incidence, severity [91, 92], and mortality attributed to COVID-19 [92, 93]. These studies concluded that those at the highest risk for severe COVID-19 matched those at the highest risk for severe vitD deficiency, including older people, darker-skinned ethnic groups, and obese people [91, 93, 94].

2.3.3 Vitamin D and immigrant clinical practice guidelines

Clinical practice guidelines (CPGs) are based on scientific evidence and provide up-to-date knowledge, increase the efficiency of the translation of research into practice, improve the effectiveness and quality of care, and decrease variations in healthcare practices [95] [96] [97].

The Institute of Medicine defined CPGs as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [95]. Currently, CPGs pertaining to vitD vary among countries and organizations in terms of their scope, targeted populations, and recommendations [98-101].

Although vitD deficiency among immigrants is a global issue that was detected more than five decades ago [3, 22, 28, 61, 102, 103], available vitD CPGs were country-specific and varied in their recommendations. Moreover, few of these publications met the criteria for guideline development, as not all were defined as CPGs, and the immigrant population is barely mentioned in the recommendations.

In recent decades, recommendations and general guidelines have become widely available to manage and accommodate health-related issues among immigrants [22, 103, 104]. These publications focused on screening, infectious diseases, mental health, chronic diseases, treatment, and immunization [22, 103, 104]. Very few of the available publications met the criteria for definition as CPGs that were inadequately systematically appraised in terms of quality [22, 103]

2.4 National Canadian data on vitamin D and immigrants

The Canadian Health Measures Survey (CHMS) is a cross-sectional population-based survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada [105]. The survey has been conducted in cycles biannually since 2007 [65, 105]. The CHMS is the first national survey with data on vitD for the Canadian population including immigrants.

Statistics Canada determined the sample size and weights to produce reliable and representative estimates at the national level for sex and age groups. The survey covered approximately 96% of the Canadian population. Each cycle collected data from sixteen collection sites spread across Canada, stratified into five regions; namely British Columbia, the Prairies (Alberta, Manitoba, and Saskatchewan), Ontario, Quebec, and the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick) [105]. All residents living in a private dwelling aged 3 to 79 were eligible for participation. Residents were excluded if they lived in the territories, on reserves, and in other Aboriginal settlements in the provinces. Moreover, the full-time members of the Canadian Forces, the institutionalized population, and residents of some remote regions were excluded [65, 105]. CHMS employs a stratified three-stage sample selection using a roster list of all persons living in the household and one or two participants were randomly selected [105].

All participants provided written informed consent for a personal interview, physical measures, and biospecimens collection. All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025) [105]. The CHMS microdata is hosted in secure centers overall in Canada. These data were accessed and analyzed at the Carleton, Ottawa, Outaouais

Local Research Data Centre (COOLRDC) in the Morisset Library at the University of Ottawa.

Strengths and limitations of CHMS data

Table 1. Strengths and limitations of CHMS data

Strengths	Limitations
• Comprehensive national data represent the Canadian population. • Exclusive data on vitD and has a large sample size of immigrants. • The data offered an accurate and representative measure of S-25(OH)D levels at the national level. • Immigrants were selected as foreign-born and identified as first-generation immigrants. • The data includes ethnocultural diversity of immigrants from more than 153 countries and represents more than 13 major ethnic groups. • The data has several clinical, physical, biological measures, and self-reported health data. • The data has other clinical indicators (e.g., melanin level) that can be used as a reliable measure of skin pigmentation. • The S-25(OH)D levels were collected over the entire year, which enabled adjustment for seasonal variations in UVB light exposure. • The data were validated against other national data such as the Canadian Community Health Survey, Census data, and the 2011 National Household Survey.	• CHMS is secondary data collected between 2012-2015. • CHMS data did not differentiate immigrants by specific immigration class or type (e.g., refugees, family class, economic migrants, or asylum seekers). • The group of native-born Canadian may be formed of second or third-generation immigrants; this resulted in a high level of heterogeneity in the reference population. • Cycles have different themes, which may result in massive missing data when more than one cycle is combined. • The date of diagnosis was not given in this data that constraints the use of important chronic disease such as kidney disease.

In this study (Chapter 3), we combined and used two CHMS datasets that were conducted between 2012 to 2015. These are cycle 3 (2012-2013) and cycle 4 (2014-2015). We found that these two cycles were the most thematically consistent of the six available 2019-CHMS cycles. The consistency was related to the availability of sociodemographic characteristics, lifestyle factors, vitD-rich foods consumption, and behavioral, environmental, and biological

determinants. We derived all variables of interest based on Statistics Canada's instructions on the cycle-specific cycle user guide, data codebook, combining more than one cycle, and the derived variable specifications [106].

The two cycles were combined to increase the sample size and provide a more stable and precise estimate of sampling variability at the national level than was possible using a single data cycle estimate. The combined response rate (response rate for all study components, such as household visits, blood samples, and activity monitor) at the Canadian level for cycle 3 was 51.7%, and that for cycle 4 was 53.7% [106, 107]. As recommended, we used bootstrap 1–bootstrap 500, full-weight or applicable weight, and the required degrees of freedom to correct variance estimations in the final analysis [106, 107]. The single-cycle weight was dropped from the dataset as it was a cycle-specific weight. The pre-specified combined full-sample weights and degrees of freedom for the two cycles were used in our analyses.

We extracted data on S-25(OH)D levels in nmol/L from the two cycles and identified four cut-offs to classify vitD status, namely: deficient status (<30); insufficient status (<50) which includes the deficient and insufficient; an accumulating value for deficient, insufficient, and sufficient (<75); and the optimal or the "no added values" (≥75) as defined IOM and other experts [28, 63, 64, 66].

We calculated the vitD-associated or related factors with the risk for developing vitD deficiency/insufficiency: immigration status, sex, age, income, education level, body mass index (BMI, kg/m2), smoking status, alcohol consumption, age at immigration, length of time in Canada, sun exposure, sunscreen use, season and month of blood sampling, clothing type, physical activity, region and country of birth, ethnicity, skin pigmentation (melanin level), use

of indoor tanning equipment, intake of vitD-rich foods, and vitD supplements/medications used.

We also examined the presence of chronic diseases identified in CHMS data as "a long-term condition diagnosed by a healthcare professional and expected to last or has already lasted six months or more.". These conditions included 24 chronic diseases and conditions (e.g., type 1 and 2 diabetes, heart disease (not limited to ischemic heart disease), and mood disorder). For this study, we considered only five chronic diseases (CDs) (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases) and two self-rated health conditions of general and mental health. Inflammatory lung diseases were a combination of CDs that had similar inflammatory characteristics (including, but not limited to chronic obstructive pulmonary disease, bronchitis, and emphysema). Six biomarkers associated with the identified CDs were also assessed: glycated hemoglobin (HbA1c), the total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL ratio), high-sensitivity C-reactive protein (hs-CRP), immunoglobulin E (IgE), ferritin, hemoglobin (Hb). Data for CDs and other clinical and biological measures, including several temporal attributes such as date of immigration and mobile clinic visit dates (e.g., blood sampling including S-25(OH)D), were used to create proxy health indicators for health deterioration.

Because of the nature and scope of this study, we tend to include only the chronic diseases of "non-skeletal health" when the date of diagnosis was given only. More specifically, we included the five-mentioned chronic diseases and exclude all others. The reasons for excluding conditions were as follows:

1- *Some of these chronic diseases were under "skeletal health" which is not in the scope of this study (e.g., osteoporosis).*

2- *Some of these chronic diseases occurred in insufficient numbers that could not be stratified and fulfill Statistics Canada's confidential policy of publishing results with small numbers, and their exclusion will not greatly impact the results given the limited number (e.g., hepatitis).*
3- *Some of these chronic diseases (e.g., kidney disease) did not have a date of diagnosis, which is essential for the analysis and interpretation that is linked to the date of immigration.*

If the date of diagnosis was not available for an eligible chronic disease (i.e., a chronic disease that is non-skeletal with a sufficient number of cases that can be published without jeopardizing the confidentiality of the data), it is considered a data limitation.

Therefore, considering the scope and the nature of this study, we tend to include the above-mentioned chronic diseases of "Diabetes, Heart disease, Cancer, Asthma, Inflammatory lung diseases" and exclude all others. Details of the complete list of 24 chronic conditions and inclusion\exclusion reasons for these conditions are presented in Table 2.

Table 2. List of 24 chronic conditions in CHMS data

Diseases and Conditions	Date of diagnosis	Skeletal disease	Insufficient number	No date of diagnosis
Diabetes (type1 & 2)	**X**			
Heart disease	**X**			
Cancer	**X**			
Asthma	**X**			
Bronchitis	**X**			
Emphysema	**X**			
COPD				**X**
Fibromyalgia		**X**		**X**
Fibromyalgia and back pain		**X**		**X**
Osteoporosis		**X**		**X**
Back pain excluding fibromyalgia and arthritis		**X**		**X**
Thyroid condition			**X**	**X**
High blood pressure				**X**
High cholesterol				**X**
Liver & gallbladder problems				**X**
Kidney disease				**X**
Stroke			**X**	**X**
Hepatitis			**X**	**X**
Mood disorder			**X**	**X**
Eating disorder			**X**	**X**
Developmental disability			**X**	**X**
Attention deficit disorder			**X**	**X**
Learning disorders			**X**	**X**
Other Phys and Mental Cond				**X**

2.5 Rationale and summary

Worldwide, a broad spectrum of studies have examined vitD and its determinants. In addition, many epidemiological studies have directed attention to studying vitD among immigrants compared with non-immigrants in the last few decades. These studies mainly aimed to identify determinants of the growing problem of vitD deficiency among immigrants. However, the designs, populations, and included vitD determinants varied among these studies.

We identified that there were fundamental limitations and knowledge gaps in previous epidemiological studies, policies, and regulatory agencies. These can be summarized in four major points. First, reasons for the healthy immigrant effect decline over time were hypothesized to be related to changes in lifestyle and other environmental factors and have not yet been explicitly identified. Although there is some evidence supporting an association between an inadequate S-25(OH)D concentration and an increased risk for CDs, the evidence is continuing to grow, and the causative nature and efficacy of vitD remain controversial. For example, there was a two-way correlation between vitD deficiency and disease outcomes (e.g., infectious diseases, rheumatoid arthritis, and obesity). In addition, available evidence comes from experimental, ecological, and observational studies, and few clinical trials focused on vitD supplementation were identified to provide causal support for such a relationship. However, no previous study has linked health deterioration over time to the growing vitD deficiency among immigrants.

Second, available studies on vitD deficiency among immigrants were country-specific and focused on individual groups with relatively small sample sizes. In addition, the immigrant populations were not clearly identified and often included more than one generation (aggregated generations). Moreover, determinants of vitD deficiency were limited or missing

essential components, not specific to immigrants, or not identified or correctly measured. For example, few studies used reliable measures to evaluate skin pigmentation, and the impact of indoor tanning on melanin levels and vitD was not investigated. In addition to age and sex variations, these variations, limitations, and drawbacks resulted in a wide range of reported S-25(OH)D across the studies (e.g., 4.9–136.2 nmol/L).

Third, although vitD deficiency among immigrants is a global issue that has been detected for more than five decades, a preliminary search indicated the available CPGs for vitD and for immigrants did not acknowledge the growing problem of vitD deficiency. There were no recommendations for immigrants included in vitD guidelines, and no vitD recommendations included in immigrant guidelines, even in the most recent and well-established guidelines. Moreover, in addition to most available guidelines not meeting the criteria for identification as CPGs, few of these CPGs met the guideline development criteria.

Fourth, there are no clear prevention strategies at Canadian national or international levels to prevent or delay the development of health deterioration among immigrants or to combat the growing problem of vitD deficiency among immigrants.

Therefore, to overcome the limitations of previous studies and reduce the knowledge gaps concerning vitD and immigrants' health, we sought to examine vitD among immigrants using a large national database that collected data for all related-vitD determinants. In addition, we investigated whether the melanin level explained the variation in the reported S-25(OH)D levels among immigrants compared with non-immigrants. Moreover, we examined whether vitD deficiency impacted immigrants' health status using the prevalence of CDs and CD-related biomarkers that deviated from standard levels as proxy indicators for health deterioration.

We planned to compare the global vitD status of immigrants with non-immigrants and between immigrant groups based on ethnicity, region, and country of birth to identify the global determinants of vitD deficiency among immigrants. Furthermore, we aimed to illustrate the results in global maps, including maps for the vitD status of immigrants and non-immigrants, for the same ethnic immigrants in different geographical regions, and maps based on migration and latitude points to northern host countries. We also planned to systematically evaluate the quality and content of the most recent available guidelines. Specifically, we sought to answer two research questions: 1) Do CPGs for immigrants' health include recommendations on vitD? and 2) Do CPGs for vitD include recommendations for immigrants?

The following three chapters (Chapters 3–5) explore the methodological implementation of different studies to tackle the above-mentioned knowledge gaps and limitations. These three chapters present five published manuscripts, one submitted manuscript, three manuscripts that are in progress, and two are planned based on the overall of the thesis findings.

References

1. WHO, *Report on the health of refugees and migrants in the WHO European region: no public health without refugee and migrant health.* 2018.
2. WHO. *Refugee and migrant health*. 2022 May 2022 [cited 2022 Oct. 2022]; Available from: https://www.who.int/news-room/fact-sheets/detail/refugee-and-migrant-health.
3. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.
4. Council on Foreign Relations. *What Is Canada's Immigration Policy?* 2022 February 9, 2022; Available from: https://www.cfr.org/backgrounder/what-canadas-immigration-policy.
5. Statistics Canada, *Immigration and Ethnocultural Diversity in Canada. National Household Survey, 2011.* Statistics Canada, 2013. **Catalogue no. 99-010-X2011001**(99): p. 23-23.
6. Statistics Canada. *Canada in 2041: A larger, more diverse population with greater differences between regions*. 2022; Available from: https://www150.statcan.gc.ca/n1/en/daily-quotidien/220908/dq220908a-eng.pdf?st=K13tiyuc.
7. Statistics Canada. *Population Projections for Canada, provinces and Territories*. 2014 [cited 2021 20/11/2021]; Available from: https://www150.statcan.gc.ca/n1/en/pub/91-520-x/91-520-x2010001-eng.pdf?st=LWFifucU.
8. Gushulak, B.D. and L.S. Williams, *National Immigration Health Policy Existing Policy, Changing Needs, and Future Directions.* CANADIAN JOURNAL OF PUBLIC HEALTH, 2004. **95**(3): p. 1-27.
9. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.
10. Dunn, J.R. and I. Dyck, *Social determinants of health in Canada's immigrant population: results from the National Population Health Survey.* 2000.
11. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
12. Hemminki, K., *Immigrant health, our health.* The European Journal of Public Health, 2014. **24**(suppl 1): p. 92-95.

13. Sanou, D., et al., *Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.

14. Vang, Z., et al., *The Healthy Immigrant Effect in Canada: A Systematic Review.* Population Change and Lifecourse Strategic Knowledge Cluster Discussion Paper Series/Un Réseau stratégique de connaissances Changements de population et parcours de vie Document de travail 2015. **3**(1): p. 4.

15. Salant, T. and S.L. Diane, *Measuring culture: a critical review of acculturation and health in Asian immigrant populations.* Social Science & Medicine, 2003. **71**: p. 71-90.

16. Zhu, L., *Depression risks and correlates among different generations of Chinese Americans: The effects of relationships with friends and relatives.* Social Sciences, 2017. **6**(2).

17. Chiswick, B.R., Y.L. Lee, and P.W. Miller, *Immigrant selection systems and immigrant health.* Contemporary Economic Policy, 2008. **26**(4): p. 555-578.

18. Fernando, G.D.M. and K. Eagan, *The deterioration of health status among immigrants to Canada.: EBSCOhost*, in *Vol. 5, No. 5, September 2010, 462478*. 2010. p. 462-478.

19. Renzaho, A.M.N., J.A. Halliday Bhsci, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review.* Nutrition, 2011. **27**: p. 868-879.

20. Kennedy, S., J.T. McDonald, and N. Biddle, *The Healthy Immigrant Effect and Immigrant Selection: Evidence from Four Countries.* 2006.

21. Hansson, E., et al., *Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement*, in *for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada*. 2010.

22. Pottie, K., et al., *Evidence-based clinical guidelines for immigrants and refugees.* CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 2011. **183**: p. E824-925.

23. Frankish, J., et al., *HEALTH IMPACT ASSESSMENT AS A TOOL FOR POPULATION HEALTH PROMOTION AND PUBLIC POLICY EXECUTIVE SUMMARY.* 1996.

24. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.

25. Beiser, M., *The International refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada*. 1993.

26. Williams, D.R., et al., *Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities.* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 69-101.

27. Chiu, M., et al., *Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-ethnic Study.* Canadian Journal of Cardiology, 2012. **28**(1): p. 20-26.

28. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

29. Eggemoen, Å.R., et al., *Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults.* BMJ open, 2013.

30. Aucoin, M., et al., *Vitamin D status of refugees arriving in Canada Findings from the Calgary Refugee Health Program.* 2013. **59**.

31. Baauw, A., et al., *Health needs of refugee children identified on arrival in reception countries: A systematic review and meta-Analysis*, in *BMJ Paediatrics Open*. 2019, BMJ Publishing Group.

32. Lips, P., et al., *Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society.* European journal of endocrinology, 2019. **180**(4): p. P23-P54.

33. Centers for Disease Control Prevention. *Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination.* . 2013; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf.

34. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

35. Gaksch, M., et al., *Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium.* PLOS ONE, 2017. **12**(2): p. e0170791-e0170791.

36. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British Journal of Nutrition, 2014. **111**: p. 23-45.

37. Spedding-Simon, *Vitamin D and Human Health*. 2015 ed. 2015, MDPI • Basel • Beijing • Wuhan: Publisher Shu-Kun Lin.

38. Stephens, W.P., et al., *Observations on the Natural History of Vitamin D Deficiency amongst Asian Immigrants.* QJM: An International Journal of Medicine, 1982. **51**(2): p. 171-188.

39. Stern, P.J., *Generational Differences.* 2002.

40. Erdman, P., et al., *CAP Laboratory Improvement Programs Accuracy-Based Vitamin D Survey Six Years of Quality Improvement Guided by Proficiency Testing.* Arch Pathol Lab Med, 2019. **143**.

41. Pilz, S., et al., *Vitamin D testing and treatment: a narrative review of current evidence.* Endocrine Connections, 2019. **8**(2): p. R27-R43.

42. Charoenngam, N., A. Shirvani, and M.F. Holick, *Vitamin D for skeletal and non-skeletal health: What we should know.* Journal of Clinical Orthopaedics and Trauma, 2019. **10**(6): p. 1082-1093.

43. Roth, D.E., et al., *Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low-and middle-income countries*. 2018, Wiley Online Library.

44. Wacker, M. and M.F. Holick, *Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation.* Nutrients, 2013. **5**: p. 111-148.

45. Shin, S.-Y., et al., *Measurement of Serum Total Vitamin D (25-OH) Using Automated Immunoassay in Comparision With Liquid Chromatography Tandem-Mass Spectrometry.* Journal of Clinical Laboratory Analysis, 2013. **27**: p. 284-289.

46. Nowson, C.A., et al., *Vitamin D and health in adults in Australia and New Zealand: a position statement.* Medical Journal of Australia, 2012. **196**(11): p. 686-687.

47. Statistics Canada, *Vitamin D blood levels of Canadians*. 2015.

48. Cranney, A., et al., *Effectiveness and safety of vitamin D in relation to bone health.* Evidence report/technology assessment, 2007(158): p. 1.

49. Bogh, M.K., *Vitamin D production after UVB: aspects of UV-related and personal factors.* Scandinavian Journal of Clinical and Laboratory Investigation, 2012. **72**(sup243): p. 24-31.

50. Carlberg, C., *Nutrigenomics of vitamin D.* Nutrients, 2019. **11**(3).

51. Atef, S.H., *Vitamin D assays in clinical laboratory: Past, present and future challenges.* The Journal of Steroid Biochemistry and Molecular Biology, 2018. **175**: p. 136-137.

52. Pham, T., *Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal.* Thesis-McGill University, 2012.

53. De Boer, I.H., et al., *25-Hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification.* Journal of the American Society of Nephrology, 2009. **20**(8): p. 1805-1812.

54. Zmijewski, M.A., *Vitamin D and Human Health.* International Journal of Molecular Sciences, 2019. **20**(1): p. 145.

55. Heaney, R.P. and M.F. Holick, *Why the IOM recommendations for vitamin D are deficient.* Journal of Bone and Mineral Research, 2011. **26**(3): p. 455-457.

56. Basit, S., *Vitamin D in health and disease: a literature review.* British Journal of Biomedical Science, 2013. **70**(4): p. 161-172.

57. Dawson-Hughes, B., *Vitamin D and muscle function.* The Journal of Steroid Biochemistry and Molecular Biology, 2017. **173**: p. 313-316.

58. British Columbia Guidelines, *Vitamin D Testing.* Clinical Practice Guidelines and Protocols in British Columbia, 2019.

59. Holick, M.F., et al., *Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline.* The Journal of Clinical Endocrinology & Metabolism, 2011. **96**(7): p. 1911-1930.

60. Adit A. Ginde, Mark C. Liu, and Carlos A. Camargo Jr, *Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004.* Arch Intern Med, 2009. **169**(6): p. 626–632-626–632.

61. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D*, in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.

62. Carlberg, C., *Vitamin D and Pigmented Skin*. 2022, Multidisciplinary Digital Publishing Institute. p. 325.

63. Dawson-Hughes, B., *Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment - UpToDate*. 2021.

64. Ross A. Catharine, et al., *DIETARY REFERENCE INTAKES Calcium Vitamin D Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board*. 2011.

65. Ng, E., *Canadian Health Measures Survey: A tool for immigrant health research?* Statistics Canada, Health Report, 2015.

66. Vieth, R., *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml).* Best Practice & Research Clinical Endocrinology & Metabolism, 2011. **25**: p. 681-691.

67. Sharma, L.K., et al., *The increasing problem of subclinical and overt hypervitaminosis D in India: An institutional experience and review.* Nutrition, 2017. **34**: p. 76-81.

68. Palacios, C., et al., *Regimens of vitamin D supplementation for women during pregnancy.* Cochrane Database of Systematic Reviews, 2019(10).

69. Henry J Woodford, A.S.B.B. and C. Stewart Pattman, *Vitamin D: too much testing and treating? Authors: Henry J Woodford , A Scott Barrett B and Stewart Pattman C ABSTRACT*. 2018.

70. Bikle, D.D., *Vitamin D Assays.* Frontiers of Hormone Research, 2018. **50**: p. 14-30.

71. Emmanuel Matabaro, N.I.E.U. and H.L. Byong, *Current Immunoassay Methods for the Rapid Detection of Aflatoxin in Milk and Dairy Products.* 2017.

72. Lai, J.K.C., et al., *Assessing vitamin D status: Pitfalls for the unwary.* Molecular Nutrition & Food Research, 2010. **54**(8): p. NA-NA.

73. Altieri, B., et al., *Vitamin D testing: advantages and limits of the current assays.* European Journal of Clinical Nutrition, 2020. **74**: p. 231-247.

74. Galior, K., et al., *10 years of 25-hydroxyvitamin-D testing by LC-MS/MS-trends in vitamin-D deficiency and sufficiency.* Bone Reports, 2018. **8**: p. 268-273.

75. Grange, R.D., et al., *Radioimmunoassay, enzyme and non-enzyme-based immunoassays*, in *British Journal of Anaesthesia*. 2014, Oxford University Press. p. 213-216.

76. Mathew, E.M., et al., *Cost-Effective HPLC-UV Method for Quantification of Vitamin D 2 and D 3 in Dried Blood Spot: A Potential Adjunct to Newborn Screening for Prophylaxis of Intractable Paediatric Seizures*, in *Chem. Pharm. Bull*. 2019. p. 88-95.

77. Rahman, A., et al., *The routine chemiluminescence assay for plasma 25-hydroxyvitamin D analysis does not overestimate the prevalence of vitamin D deficiency in adolescents.* 2020.

78. Keyfi, F., et al., *Evaluation of 25-OH vitamin D by high performance liquid chromatography: validation and comparison with electrochemiluminescence.* 2018.

79. Holick, M.F., *The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health INTRODUCTION: HISTORICAL PERSPECTIVE.* Public Health Reviews, 2010. **32**(1): p. 267-283.

80. Thuesen, B., et al., *Determinants of vitamin D status in a general population of Danish adults.* Original Full Length Article, 2011.

81. Thacker, S.B., et al., *Measuring the public's health.* Public health reports, 2006. **121**(1): p. 14-22.

82. Chowdhury, R., et al., *Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies.* Bmj, 2014. **348**.

83. Sun, Y.-Q., et al., *Serum 25-hydroxyvitamin D level, chronic diseases and all-cause mortality in a population-based prospective cohort: the HUNT Study, Norway.* BMJ open, 2017. **7**(6): p. e017256.

84. Bischoff-Ferrari, H.A., et al., *Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes.* The American journal of clinical nutrition, 2006. **84**(1): p. 18-28.

85. Glendenning, P. and C.A. Inderjeeth, *Controversy and consensus regarding vitamin D: Recent methodological changes and the risks and benefits of vitamin D supplementation.* Critical reviews in clinical laboratory sciences, 2016. **53**(1): p. 13-28.

86. Chu, F., et al., *Serum 25-Hydroxyvitamin D Concentrations and Indicators of Mental Health: An Analysis of the Canadian Health Measures Survey.* Nutrients, 2017. **9**(10): p. 1116-1116.

87. Dong, J.-Y., et al., *Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies.* Nutrients, 2013. **5**(9): p. 3551-3562.

88. Littlejohns, T.J., et al., *Vitamin D and the risk of dementia and Alzheimer disease.* Neurology, 2014. **83**(10): p. 920-928.

89. de Barros Viana, M., et al., *COVID-19 in age-related neurodegenerative diseases: is there a role for vitamin D3 as a possible therapeutic strategy?* Reviews in the Neurosciences, 2021. **32**(2): p. 235-247.

90. Prietl, B., et al., *Vitamin D and immune function.* Nutrients, 2013. **5**(7): p. 2502-2521.

91. Cristian Ilie, P., S. Stefanescu, and L. Smith, *The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality.* Aging clinical and experimental research 2020. **32**(7): p. 1195-1198.

92. Ghasemian, R., et al., *The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis.* medRxiv, 2021: p. 2020.06.05.20123554-2020.06.05.20123554.

93. Mercola, J., W.B. Grant, and C.L. Wagner, *Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity.* Nutrients, 2020. **12**(11): p. 3361-3361.

94. Meltzer, D.O., et al., *Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.* JAMA network open, 2020. **3**(9): p. e2019722-e2019722.

95. Graham, R., et al., *Clinical Practice Guidelines We Can Trust*. Clinical Practice Guidelines We Can Trust. 2011.

96. Kredo, T., et al., *Guide to clinical practice guidelines: the current state of play*. International Journal for Quality in Health Care, 2016. **28**(1): p. 122-122.

97. Shiffman, R.N., et al., *Bridging the guideline implementation gap: a systematic, document-centered approach to guideline implementation.* Journal of the American Medical Informatics Association, 2004. **11**(5): p. 418-426.

98. Rusinska, A., et al., *Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies-2018 Update.* Frontiers in endocrinology, 2018. **9**: p. 246.

99. NICE, *Vitamin D: supplement use in specific population groups.* NICE, 2014: p. 1-55.

100. Alberta Medical Association, *Toward Optimized Practice (TOP) Working Group for Vitamin D. Guideline for Vitamin D Testing and Supplementation in Adults. Edmonton, AB: Toward Optimized Practice.* 2012.

101. Dai, Z., et al., *Methodological quality of public health guideline recommendations on vitamin D and calcium : a systematic review protocol.* BMJ Open, 2019. **9**(11): p. e031840-e031840.

102. Cashman, K.D., et al., *Vitamin D deficiency in Europe: pandemic?* The American journal of clinical nutrition, 2016. **103**(4): p. 1033-44.

103. Agbata, E.N., et al., *Migrant Healthcare Guidelines: A Systematic Quality Assessment.* Journal of Immigrant and Minority Health, 2019. **21**(2): p. 401-413.

104. Swinkels H, P.K., Tugwell P, Rashid M, Narasiah L, *Development of guidelines for recently arrived immigrants and refugees to Canada: Delphi consensus on selecting preventable and treatable conditions.* Canadian Medical Association journal = journal, 2011. **183**(12): p. E928-32.

105. Day, B., et al., *Canadian Health Measures Survey: ethical, legal and social issues*, in *Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé*. 2007. p. 37-51.

106. Statistics Canada. *Canadian Health Measures Survey (CHMS) CHMS User Guide Cycle3* 2015; Available from: https://usermanual.wiki/Pdf/CHMSUserGuideCycle3E.484319040/view.

107. Statistics Canada, *Canadian Health Measures Survey (CHMS), Cycle 4*. 2014.

Chapter 3: Analysis of national data (CHMS) on vitamin D and first-generation immigrants

Chapter overview

Similar to other immigrants worldwide, Canadian immigrants (foreign-born) have lower levels of S-25(OH)D compared to native-born Canadian. Healthy immigrant effect (advantage) and deterioration over years of settlements are also well documented.

In this chapter, cycle 3 (2012-2013) and cycle 4 (2014-2015) of CHMS data were used. It involves a total sample size of 11,579 participants including a large population of immigrants from 153 countries and more than 13 ethnic groups. CHSM is the first Canadian data on vitD and immigrants, collected in cross-sectional survey design, and validated against other national data. In addition to several clinical, physical, biological measures, and self-reported health data, the data has other clinical indicators (e.g., melanin level) that can be used as a reliable measure of skin pigmentation. The results are based on a high-quality population-based national survey conducted every two years with appropriate weighting to accurately represent all of Canada.

Chapter 3 includes three studies to shed light on the growing problem of lower levels of S-25(OH)D among Canadian immigrants to address the first set of thesis research questions:

- What are the determinants of vitD among first-generation immigrants in Canada?
- Do all Canadian immigrants have the same risk of vitD deficiency?
- Do melanin levels varying between immigrants based on ethnicity and country of origin?

- Do melanin levels explain the variations in S-25(OH)D between immigrants and the native-born Canadians?
- Is there any association between S-25(OH)D levels with CDs and/or CDs-related biomarkers?

Chapter 3 contains three manuscripts (**Sections 3.1–3.3**), all have been published in a peer-review journal. A short description for each manuscript as follows:

Chapter contents

Section 3.1 describes the levels and status of S-25(OH)D among first-generation immigrants from different ethnic groups and origins compared to native-born Canadian.

Section 3.2. investigate the relationship between melanin levels and vitamin D among first-generation immigrants from different ethnic groups and origins compared to native-born Canadian.

Section 3.3 presents the health status of first-generation immigrants compared to native-born Canadian and investigates the possible association between vitamin D and CDs and CD-related biomarkers.

3.1 Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins

Section overview

This is the first national Canadian study to report vitD status and its determinants among first-generation immigrants from different ethnic groups and origins compared with non-immigrants. The lower S-25(OH)D levels in this study was consistent with global evidence suggesting that immigrants in Western countries have lower S-25(OH)D levels than non-immigrant populations. The strongest explanatory factors predicting low S-25(OH)D levels among immigrants in Canada were ethnic background, not exposed to a sunny/warm climate two months before vitD's test, and low consumption of dairy product. The length of stay in Canada was positively associated with S-25(OH)D levels.

Manuscript status

This manuscript has been published: *Nutrients 2021, 13, 2702.*

https://doi.org/10.3390/nu13082702

Said Yousef*, Douglas Manuel, Ian Colman, Manny Papadimitropoulos, Alomgir Hossain, MoezAlIslam Faris, and George A. Wells.

Author contributions

S.Y. and G.A.W. conceived the study. With close supervision from G.A.W., S.Y. managed the data, verified the analytical methods, and prepared the tables and figures. A.H. verified the underlying data at the Research Data Center. S.Y. and M.F. interpreted the results and prepared the final draft. All authors including D.M., I.C. and M.P. contributed to the design and analysis

of the research, and the substantive review of the manuscript. All authors have read and agreed to the published version of the manuscript.

Related thesis appendices

Appendix A3:

The PDF of the published manuscript is presented in Appendix A3.1.

Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey

Said Yousef*; Douglas Manuel; Ian Colman; Manny Papadimitropoulos; Alomgir Hossain; MoezAlIslam Faris; and George A Wells

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Douglas Manuel, MD, MSc.
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

One in five Canadians are first-generation immigrants. Evidence suggests the baseline risk for vitamin D (vitD) deficiency is increased among immigrants who move from equatorial to northern countries. We investigated the prevalence and determinants of vitD deficiency/insufficiency among first-generation immigrants compared with native-born Canadians and identified explanatory covariables. We used a cross-sectional design with data from the national Canadian Health Measures Survey (Cycles 3 and 4) (11,579 participants aged 3–79 years). We assessed serum 25-hydroxyvitamin D (S-25(OH)D) levels, sociodemographic and environmental factors, immigration status, length of time in Canada, vitD-rich food intake, ethnicity, and place of birth. Immigrants had lower mean S-25(OH)D than non-immigrants (51.23 vs. 62.72 nmol/L, $P<0.001$). Those with younger age at the time of immigration (<18 years) had a high risk for low vitD, and S-25(OH)D levels increased with the length of time they had lived in Canada. The highest deficiency levels were in immigrants born in Morocco, India, and Lebanon compared with native-born Canadians. Ethnicity was the factor most strongly associated with S-25(OH)D. Compared with the white ethnic grouping, the Japanese had the highest level of vitD deficiency, followed by Arabs and Southeast Asians. Ethnic variations, dietary intake, and lifestyle factors are the main predictors of/explanatory factors for vitD status among Canadian immigrants.

Keywords: vitamin D; serum 25-hydroxyvitamin D; first-generation immigrants; ethnicity; melanin; dietary intake.

1. Introduction

Vitamin D (vitD) plays a crucial role in physiological functions, including skeletal and non-skeletal health [1]. Vit D has two main metabolites, namely 25-hydroxyvitamin D (25-OH) and 1, 25 dihydroxy vitamin D. The dietary sources (vitamin D2 or ergocalciferol) and the animal-based foods (vitamin D3 or cholecalciferol) are the two main forms of vitamin D found in the human body [2-4]. The primary source of vitD in the human body, however, is through skin exposure to sunlight (cutaneous synthesis of vitD3)[2, 5]. Vitamin D2 and D3 are considered to have equal biological value. The total serum 25-hydroxyvitamin D (S-25(OH)D) concentration is the sum of the 25(OH) D2 and 25(OH) D3 concentrations [6]. The concentration of S-25(OH)D represents the combined contributions of the cutaneous synthesis and dietary intake of vitD and is considered the top clinical marker for overall S-25(OH)D level [7-9]. The S-25(OH)D is expressed in nanomoles per liter (nmol/L) and has a stable half-life (up to 3 weeks) in the human body [7].

The mean of S-25(OH)D (nmol/L) and/or the ranges for the thresholds (a deficiency, < 25 - 30 nmol/L; insufficiency, 25 - 49 nmol/L; sufficiency, ≥ 50 - < 75 nmol/L) were commonly reported and used in studies to describe the status of vitD [8]. The insufficient status (<50 nmol/L) is more frequently used to describe hypovitaminosis D [10]. However, the optimal S-25(OH)D concentration for skeletal health is controversial. The Institute of Medicine (IOM) recommends maintaining S-25(OH)D concentration levels above 50 nmol/L, whereas other experts favor the concentration between 50 to 100 nmol/L [11-13].

Multiple factors affect the body's ability to synthesize vitD, including dietary intake, coexisting disease conditions (especially liver and kidney diseases), and sun-related vitD production (e.g., sun exposure)[8, 9, 14, 15]. Other implicated factors include

sociodemographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and latitude), cultural and religious aspects (e.g., clothing and prolonged breastfeeding time), and health and genetic factors (e.g., melanin levels and obesity)[8, 10, 16]. A global review of evidence from six regions (Europe, North America, Latin America, Asia, the Middle East/Africa, and Oceania) showed the leading risk factors for vitD deficiency were older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, poor dietary habits, and absence of vitD fortification [10].

Hypovitaminosis D is a worldwide public health problem to which immigrants are particularly vulnerable, with a high baseline risk among populations with darker skin who migrate from equatorial regions to northern latitudes [17, 18]. Migration is considered a significant risk factor for low S-25(OH)D levels attributable to lifestyle and environmental changes, including dietary intake, physical activity, sun exposure, clothing, and a move from low to high latitude countries [8, 17, 18]. Immigrants in Canada and other Western countries have a high prevalence of vitD deficiency and insufficiency compared with Western people, with a deficiency prevalence of 19.3%–80% among different ethnic minorities [8, 15, 19]. A meta-analysis of 36 studies reported variation in vitD deficiency among dark-skinned immigrants was attributable to the length of residence in the host country, age at immigration, nutritional barriers, and geographic origins and ethnicities of the studied populations [18]. Moreover, the estimated pooled prevalence of vitD deficiency was 77% (95% confidence interval [CI], 70%–83%) after adjustment for latitude [18].

The immigrant population in Canada has increased in recent decades. One in five Canadians is foreign-born, with these people originating from over 200 ethnic groups or origin countries

[20]. Research evidence suggests the presence of significant differences in sociocultural contexts and various outcomes between first-generation and second or third generation immigrants [21, 22]. Moreover, researchers recommended studying and comparing ethnic groups from the same generation [21-24].

There is a paucity of information about the status of vitD among Canadian immigrants from different ethnic groups and origins. Therefore, we intend to study first-generation immigrants as identified in the Canadian Health Measures Survey (CHMS) data (foreign-born) to investigate vitD status among immigrants compared with the non-immigrant (native-born) population. Most of the previous studies on immigrants' vitamin D involved aggregated generations of immigrants (first, second, or more generations), resulting in high heterogeneity in the study population. Moreover, they focused on specific groups from relatively few ethnicities or few countries of origin. However, this study is the first to report vitD status among large sample of first-generation immigrants from 13 major ethnic groups and who were migrated from 153 countries of origin compared with white ethnic group and native-born Canadians.

The study aimed to estimate the prevalence of vitD status and the leading determinants of vitD deficien-cy/insufficiency among immigrants from different ethnicities and regions/countries of birth compared with white and native-born Canadians. Moreover, to understand the effects of the environment, lifestyle, and acculturation on immigrants' vitD, we aimed to investigate vitD status to the length of time after immigration. We hypothesized that significant differences exist in vitD status between immigrant and non-immigrant Canadians, with immigrants having lower vitD status.

2. Materials and Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was adopted in planning, implementing, and reporting this study [25].

2.1 Study design and participants

The CHMS is a cross-sectional population-based survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada [26]. The CHMS provided the first national data on vitD for the Canadian population including immigrants [26]. The CHMS was executed in cycles biannually. Compared to the 2006 Census data and the 2011 National Household Survey, CHMS data has unique information in direct physical health measures, representing the Canadian immigrant population, and addressing the gaps in their existing national information [27].

This study used data for Cycles 3 (2012–2013) and 4 (2014–2015) of CHMS data, which included randomly selected individuals aged 3–79 years [26]. Cycles-3 and -4 were selected as being the most thematic consistent Cycles in reporting vitD -rich foods and other vitD determinants than the other Cycles of CHMS data. Therefore, we combined Cycles 3 and 4 based on instructions provided by Statistics Canada. By merging the two Cycles, we aimed to provide a larger sample size and increase the number of primary sampling units to allow for greater precision in estimating small prevalence and providing more detailed analyses.

For each Cycle, Statistics Canada determined the sample size to produce reliable and representative estimates at the national level for sex and age groups. The survey covered approximately 96% of the Canadian population, each Cycle collected from sixteen collection sites spread across Canada, and stratified into five regions; namely British Columbia, the Prairies (Alberta, Manitoba, and Saskatchewan), Ontario, Quebec, and the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick). A

dwelling stratification stage was applied and followed by a roster list of all persons living in the household, and individuals aged 3 to 79 years were randomly selected [26]. All participants provided written informed consent, and the CHMS survey was approved by the Health Canada Research Ethics Board [26].

The CHMS sample population weight was adjusted for age group and sex across Canada's five standard geographic regions [27]. It is worth mentioning that except for the total number of subjects included in the analysis, the number of participants in each group and the unweighted results cannot be published due to Statistics Canada's restrictions policy, thus the results are presented as weighted results. Detailed information about merging the two cycles and the CHMS data is presented in Appendix I and on the Statistics Canada website (http://www.statcan.gc.ca) [28, 29].

2.2 Measures

The S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd, Stillwater, Minnesota, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. Data for S-25(OH)D in the two cycles were extracted and used as the outcome-dependent factors.

We used four cut-offs for S-25(OH)D to identify vitD status as follows: (<30 (nmol/L); (<50 (nmol/L); (<75 (nmol/L); and (≥75 (nmol/L). First, <30 nmol/L is used to identify deficient people. Second, (<50 nmol/L) is a cut-off for the insufficient 25(OH) D, which includes the deficient and insufficient people (it is an accumulating value and not range for the insufficient people). Third, (<75 nmol/L) is a cut-off and accumulating value for deficient, insufficient, and sufficient. Fourth (≥75 (nmol/L), is the "no added value" or the "optimal" as defined by IOM or other experts [8, 11-13]. The remaining last two cut-offs (<75 nmol/L and ≥75 nmol/L)

cover 100% of the total population. We assumed that reporting the prevalence of vitD deficiency, insufficiency, sufficiency, and the no added value or optimal categories using these cut-offs is important for clinicians and readers to see the proportion of participants under each stratified category. Moreover, we used ranges of S-25(OH)D for the above-mentioned cut-offs (<30 nmol/L; 30-49 nmol/L; 50-74 nmol/L and ≥75 nmol/L) for sub-groups of participants.

Independent variables were factors associated with the risk for developing vitD deficiency/insufficiency: immigration status, sex, age, income, education level, body mass index (BMI, kg/m^2), smoking status, alcohol consumption, age at immigration, length of time in Canada, sun exposure, sunscreen use, season and month of blood sampling, clothing type, physical activity, region and country of birth, ethnicity, skin pigmentation (melanin level), intake of vitD-rich foods, and vitD supplements/medications used.

We created BMI norms for adults aged ≥18 years according to Health Canada's national standards for weight classification [30]. For children aged 3–17 years, body weight classification was based on World Health Organization percentiles [31]. We used the Canadian Physical Activity Guidelines index to classify participants (aged 5–17 years and ≥18 years) as meeting/not meeting physical activity recommendations [32]. The season of blood sampling was categorized by the month of testing: winter (December–February), spring (March-May), summer (June–August), and fall (September–November). Region of birth was classified using five major regions based on the number of participants: Canada and North America; South/Central America and the Caribbean; Europe; Africa; and Asia. We used Statistics Canada's geographic classifications to identify the country of birth (153 countries; Appendix I), and selected the top 20 countries based on the number of participants (≥30 participants from each) to include in the analysis. These countries were Canada, China, the US, France, Jamaica,

the UK, Algeria, Mexico, Pakistan, the Netherlands, India, the Philippines, Romania, Hong Kong, Germany, Colombia, Morocco, Italy, Iran, and Lebanon. All other countries were grouped into one category (Others). The 153 countries (excluding Canada) were also combined in another category to represent all immigrants. Statistics Canada identifies ethnicity as white and non-white. The non-white group included different major ethnic groups; namely Aboriginal, South Asian, Chinese, Black, Filipino, Latin American, Arab, South East Asian, West Asian, Korean, Japanese, multiple ethnicities, and others. As reported by Statistics Canada, melanin levels were used as an indicator for skin pigmentation, with higher ranks indicating darker skin.

The steps used to combine the two cycles and to calculate the variables of interest are described in Table A1, Appendix I.

2.3 Statistical analyses

We summarized the data using numerical and graphical descriptive statistics. All statistical comparisons used the mean (standard error, SE) for continuous variables and proportions with 95% CIs for categorical variables. Data were stratified for analysis based on the variables of interest. To account for the unequal probability of selection and represent an accurate estimate of the Canadian population, we used the survey command, recommended sample weight, and degrees of freedom in the analyses. All results were weighted values. We used continuous values for S-25(OH)D in the linear regression models. A univariate analysis was used to identify independent covariates. Multivariable analyses were performed to clarify the relationship between vitD status and immigration status and highlight the factors most strongly associated with lower concentration levels of S-25(OH)D among immigrants.

We used the backward elimination method in a linear regression model adjusted for several independent covariates; namely age, sex, household income, education, BMI, season, sun exposure, sunscreen, country of birth, melanin levels, ethnicity, vitD medication and supplements, and food consumption variables. In our analysis, we applied several evaluation models. In which we determined, by excluding variables with a high percentage of missing data (e.g., margarine consumption) and variables that are influenced by S-25(OH)D levels (e.g., serum calcium), improvements in the model's estimation which better represents the study population compared to other models. Statistical significance was set at $P \leq 0.05$. Analyses were performed using SPSS version 26.0. (IBM Corp., Armonk, NY) and Stata version 16.0 (StataCorp, College Station, Texas).

3. Results

3.1 Study description and participants characteristics

The analyses were based on the total number of participants in both cycles. The combined response rate at the Canadian level (response rate for all study components like the household visit, blood samples, and activity monitor) for Cycle-3 was 51.7%, and Cycle-4 was 53.7% [33, 34]. Demographic characteristics for the two cycles are presented in Table A2, Appendix II.

There were 11,579 participants (5,785 from Cycle-3 and 5,794 from Cycle-4) aged 3–79 years, with a mean (standard error [SE]) age of 39.23 (0.085) years. S-25(OH)D levels were available for 11,009 participants and were normally distributed with an overall weighted mean of 60.28 nmol/L. Nearly 10.30% of Canadians were vitD deficient, 36.4% had insufficient vitD, 76.1% had sufficient vitD, and 23.90% had optimal vitD status.

Table 1 presents the main characteristics of immigrant and non-immigrant Canadians. Immigrants represented 21.9% of the Canadian population (about 53% female) and the majority were of non-white ethnicity. Compared with the non-immigrant population, they were older (overrepresented in the group aged ≥18 years) and had lower household income, smoking, alcohol consumption, BMI (obesity), sun exposure during peak time, and sunscreen use. However, immigrants were more likely to have higher education levels, wear concealing clothing, and have traveled to sunny\warm climates in the two months before blood sampling than non-immigrants.

The weighted mean melanin level (index values) was higher among immigrants than non-immigrants (17.08 vs. 16.29, P=0.004). Immigrants also had lower household income, and serum calcium and phosphorus levels than non-immigrants. Despite the high statistical difference of calcium (P=0.004) and phosphorus (P=0.006), the biological significance of the mean differences between immigrants and non-immigrants for calcium (2.40 vs. 2.42, respectively) and phosphorus (1.32 vs. 1.36, respectively) were negligible (Table 1). Non-immigrants reported more frequent consumption of vitD-rich foods (red/processed meats, liver, milk, cheese, dairy products, fortified margarine, and fatty fish) (Table A3, Appendix II).

Table 1. Weighted prevalence of immigrants and non-immigrants by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures Survey data.

		Non-Immigrants (78.9%), %	Immigrants (21.9%), %	All participants (100%), %	P-value
Sex	Female	49·37	52·85	50·13	0·142
Age (years)	<5	2·84	0·42	2·31	<0·001
	5–11	9·37	3·38	8·05	
	12–17	8·20	4·57	7·41	
	18–64	69·10	75·41	70·48	
	>64	10·49	16·22	11·75	
Household income (CAD)	<50000	33·15	43·93	35·51	0·008
	50000–100000	37·07	34·65	36·54	
	>100000	29·79	21·43	27·95	
Education	>Secondary school	47·26	64·63	51·07	<0·001
BMI (kg/m2)	Underweight	2·19	2·34	2·22	0·023
	Normal weight	41·40	41·75	41·48	
	Overweight	30·21	37·01	31·70	
	Obese	26·21	18·89	24·60	
Ethnic group	Non-white	11·76	62·67	22·91	<0·001
VitD-supplement and/or analog use	Yes	5·39	4·84	5·27	0·664
Smoking status	Current smoker	22·65	14·75	20·79	0·003
Alcohol	Current drinker	82·90	65·03	78·69	<0·001
Meet the physical activity recommendations	Yes	35·41	30·17	34·21	0·127
Sun exposure (10 am to 4 pm)	≥30 minutes\day	91·21	78·59	88·46	<0·001
Sunscreen use	Yes	73·94	58·57	70·64	<0·001
Clothing	Typically covered	34·66	52·54	38·51	<0·001
Traveled to sunny/warm climate	Yes	10·56	16·48	11·85	0·018
Weighted means		**Mean (SE)**	**Mean (SE)**	**(95% CI)**	**P-value**
	Age (years)	37·51 (0·26)	45·17 (0·58)	(−9·05, −6·26)	<0·001
	Income (CAD)	91985 (3831)	76317 (4004)	(8087, 23248)	<0·001
	Calcium (mmol/L)	2·42 (0·00)	2·40 (0·01)	(0·01, 0·04)	0·004
	Phosphorus (mmol/L)	1·36 (0·01)	1·32 (0·01)	(0·01, 0·06)	0·006
	Melanin (index values)	16·29 (0·29)	17·08 (0·25)	(−1·29, −0·28)	0·004

BMI, body mass index; CAD, Canadian dollars; SE, standard error; CI, confidence interval.

P-value: $P \leq 0{\cdot}05$.

3.2 S-25(OH)D concentration and VitD status by sociodemographic, lifestyle, and immigration features

Table 2 shows the weighted mean S-25(OH)D levels and vitD status by sociodemographic and lifestyle factors. Youth aged 12–17 years had the lowest S-25(OH)D levels. There were significant differences in sex, BMI (obesity), vitD supplement/medication use, sunscreen use, sun exposure during peak time (<30 minutes\day), and traveling to a sunny/warm climate in the two months before blood sampling. Differences were also found in income, smoking, alcohol consumption, physical activity, and clothing type were also found different as shown in Table III (Appendix II).

Immigrants had lower mean S-25(OH)D levels than non-immigrants (62.72 vs. 51.23 nmol/L, P<0.001). Age at immigration was associated with 25(OH)D levels; younger generations (<18 years) had a higher risk for lower vitD than older people (≥18 years). Moreover, years of residency after immigration was associated with S-25(OH)D levels, especially at 5 and 10 years, indicating that immigrants had higher S-25(OH)D levels the longer they had lived in Canada. The mean S-25(OH)D level was higher among sunscreen users than non-users (62.86 vs. 54.78 nmol/L, P<0.001).

Nearly 64% of participants had insufficient S-25(OH)D levels. VitD deficiency was twice as common among immigrants as non-immigrants. Moreover, compared with non-immigrants, more immigrants had insufficient vitD (52.82% vs. 31.75%) and fewer had optimal vitD (13.89% vs. 26.83%; P<0.001). The more years immigrants had lived in Canada, the greater the proportion with optimal levels at 5 (15.41% vs. 7.65%, P=0.002) and 10 (17.37% vs. 7.95%, P=0.022) years after immigration (Table 2). The S-25(OH)D and vitD status by

household income, education, smoking habits, alcohol consumption, physical activity, pregnancy, and clothing type are presented in Table A4, Appendix II.

Table 2. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D status			
		Mean (SE)	**(95% CI)**	**P-value**	**<30(nmol/L (10.3%), %**	**<50(nmol/L (36.4%), %**	**<75(nmol/L (76.1%), %**	**≥75(nmol/L (23.9%), %**
Immigration status	Non-immigrant†	62·72 (1·73)	-		7·82	31·75	73·21	26·83
	Immigrant	51·23 (1·41)	(8·37, 14·62)	<0·001	19·01***	52·82***	86·11	13·89***
Age at immigration (years)	<18†	46·54 (1·63)	-		19·17	64·04	91·37	8·63
	≥18	56·33 (2·34)	(−15·14, −4·44)	0·001	18·80	41·23**	80·76	19·24**
5 years after immigration	≤5†	45·94 (2·22)	-		19·55	62·54	92·35	7·65
	>5	52·77 (1·73)	(−12·58, −1·08)	0·022	18·59	50·04*	84·59	15·41*
10 years after immigration	≤10†	47·03 (1·83)	-		19·55	59·83	92·05	7·95
	>10	53·98 (1·83)	(−11·79, −2·12)	0·007	18·59	48·26	82·63	17·37**
Sex	Male†	57·92 (1·67)	-		11·13	39·65	79·62	20·38
	Female	62·53 (1·82)	(−6·30, −2·93)	<0·001	9·45	33·04***	72·58	27·42***
Age group (years)	<5	69·94 (1·64)	(−13·94, −9·01)	<0·001	1·99	15·70	67·1	32·9
	5–11	62·49 (2·16)	(−5·91, −2·29)	<0·001	4·04	27·41	77·9	22·1
	12–17	55·76 (1·93)	(0·44, 4·81)	0·021	10·49	40·38	84·36	15·64
	18–64†	58·45 (1·81)	-		12·1	39·79	78·24	21·76
	>64	71·07 (1·20)	(−15·63, −9·55)	<0·001	4·59	22·39***	58·69	41·31***
BMI (kg/m2)	Underweight	62·19 (4·05)	(−5·82, 7·51)	0·795	12·65	33·0	71·07	28·93
	Normal weight†	63·03 (2·04)	-		9·22	31·79	73·07	26·93
	Overweight	61·02 (1·68)	(−0·56, 4·58)	0·119	7·91	35·32	75·24	24·76
	Obese	54·48 (1·74)	(5·50, 11·60)	<0·001	15·25***	45·15***	82·36	17·64**
VitD-supplement and/or analog use	No†	56·97 (1·74)	-		40·52		80·56	19·44
	Yes	83·46 (5·25)	(−35·92, −17·06)	<0·001	9·80***		43·16	56·84***
Sun exposure (10 am to 4 pm)	<30 minutes\day†	55·92 (2·20)	-		15·58	48·72	76·51	23·49
	≥30 minutes\day	60·82 (1·69)	(−7·81, −1·99)	0·002	9·60**	34·65***	76·04	23·96
Sunscreen use	Never†	54·78 (1·85)	-		15·04	48·05	80·92	19·08
	Always, occasionally	62·86 (1·74)	(−10·16, −5·99)	<0·001	7·87***	30·23***	73·99	26·01***
Traveled to sunny/warm climate	No†	59·33 (1·83)	-		10·81	37·99	77·59	22·41
	Yes	67·03 (2·10)	(−11·85, −3·54)	0·001	6·49	23·71***	65·08	34·92***

Note: Following the Statistics Canada guideline, some cells merged due to the low number of participants.

† Reference value; SE, standard error; CI, confidence interval; BMI, body mass index.

P-values: * $P \leq 0{\cdot}05$; ** $P \leq 0{\cdot}01$; *** $P \leq 0{\cdot}001$.

3.3 S-25(OH)D concentration and VitD status by participants' ethnicity and country of origin

Differences were observed in mean S-25(OH)D levels between all ethnic groups compared with the white grouping (mean 64.48 nmol/L), except for the West Asian and Korean groups (Table 3). The lowest mean was reported for the Japanese (33.16 nmol/L; $P<0.001$), followed by Arabs (37.14 nmol/L; $P<0.001$), and Southeast Asians (40.92 nmol/L; $P<0.001$). Compared with the white grouping (6.61%), more than half (55%) of the Japanese ethnic group had vitD deficiency, with similar proportions found for Arabs (52%) and Southeast Asians (41.1%). Moreover, the Japanese had the highest insufficiency level (85%), followed by Koreans (81.0%), and Southeast Asians (73.8%). The ranges for insufficiency (30-49 nmol/L) and sufficiency (50-74 nmol/L) for each ethnic group are also presented in Figure A1, Appendix II.

Table 3. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by ethnicity using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D status			
		Mean (SE)	**(95% CI)**	**P-value**	**<30(nmol/L (10.3%), %**	**<50(nmol/L (36.4%%), %**	**<75(nmol/L (76.1%), %**	**≥75(nmol/L (23.9%), %**
White†		64·48 (1·73)	-		6·61	29·10	71·25	28·75
Non-white		47·67 (1·31)	(13·85, 19.77)	<0·001	21·09***	60·49***	90·39	9·61***
	Aboriginal	55·55 (1·77)	(4·36, 13.50)	0·001	10·63	40·35**	82·51	17·49*
	South Asian	45·56 (2·48)	(13·83, 24·02)	<0·001	22·11***	66·73***	91·28	8·72***
	Chinese	46·03 (1·56)	(14·17, 22·74)	<0·001	17·18***	61·84***	94·89	5·11***
	Black	43·82 (2·96)	(15·07, 26·26)	<0·001	28·87***	67·72***	91·73	8·27***
	Filipino	49·39 (3·93)	(5·90, 24·29)	0·003	7·51	58·85*	90·41	9·59***
	Latin American	52·64 (2·87)	(5·20, 18·50)	0·001	13·43	38·66	92·13	7·87*
	Arab	37·14 (4·62)	(18·15, 36·54)	<0·001	51·98***	72·17***	94·40	5·60***
	Southeast Asian	40·92 (4·43)	(13·88, 33·24)	<0·001	41·08***	73·84***	91·19	8·81**
	West Asian	53·74 (6·64)	(−3·29, 24·78)	0·127	13·83	58·27**	83·35	16·65
	Korean	44·26 (15·06)	(−10·07, 50·51)	0·180	25·12*	81·04***	18·96	
	Japanese	33·16 (8·59)	(14·12, 48·52)	0·001	55·30***	86·27***	13·83	
	Multiple ethnicities	53·04 (2·44)	(6.45, 16.44)	<0·001	14·48**	46·58***	88·83	11·17***
	Other ethnicities	50·02 (5·17)	(3·33, 25·61)	0·013	62·13***	88·36	11·64	62·13***

Note: Following the Statistics Canada guideline, some cells merged due to the low number of participants.

†Reference value; SE, standard error; CI, confidence interval. P-values: * P≤0·05; ** P≤0·01; *** P≤0·001.

Table 4 highlights the marked differences among those born in Africa, Asia, and South/Central America, and Caribbean regions. The highest rates of deficient and insufficient vitD were found among immigrants from Africa (31.2% and 68.6%, respectively) and Asia (24.5% and 69.7%, respectively) compared with those born in Canada and North America (7.7% and 31%, respectively). The ranges for insufficiency (30-49 nmol/L) and sufficiency (50-74 nmol/L) for the above mentioned five regions are also presented in Figure A2, Appendix II.

The highest mean S-25(OH)D level was found in those born in the Netherlands, followed by the UK and Germany (72.7, 68.9, and 68.5 nmol/L, respectively). The lowest mean levels of S-25(OH)D were found in those from Algeria (34.7 nmol/L, $P<0.001$), Lebanon (39.4 nmol/L, $P=0.008$), and Morocco (39.4 nmol/L, $P=0.003$). The highest deficient levels were found in those from Morocco (55.9%), India (34.4%), and Lebanon (about 30%), with the highest insufficient levels in those from Algeria (87.9%), Romania (80.7%), and Lebanon (78.7%). The ranges for insufficiency (30-49 nmol/L) and sufficiency (50-74 nmol/L) for each birth country are also presented in Figure A3, Appendix II.

Table 4. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by geographical region and country of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D status			
		Mean (SE)	**(95% CI)**	**P-value**	**<30(nmol/L (10.3%), %**	**<50(nmol/L (36.4%%), %**	**<75(nmol/L (76.1%), %**	**≥75(nmol/L (23.9%), %**
Region of birth	Canada and North America†	63·10 (1·74)	-	-	7·66	30·95	72·74	27·26
	South/Central America, and the Caribbean	53·20 (3·13)	(2·47, 17·33)	0·011	14·65	43·29	86·51	13·49
	Europe	62·61 (1·83)	(−2·98, 3·95)	0·775	8·62	31·24	77·46	22·54
	Africa	42·74 (3·50)	(13·08, 27·64)	<0·001	31·16***	68·55***	90·21	9·79**
	Asia	43·67 (1·67)	(15·51, 23·34)	<0·001	24·50***	69·67***	93·41	6·59***
Country of birth	Canada†	63·23 (1·74)	-		7·45	30·73	72·64	27·36
	China	48·62 (2·08)	(10·21, 19·01)	<0·001	10·53	63·14***	91·50	8·50***
	USA	58·67 (4·07)	(−-4·36, 13·47)	0·301	15·44*	39·01	75·69	24·31
	France	56·98 (5·19)	(−-4·17, 16·67)	0·226	34·10		90·52	9·48
	Jamaica	51·72 (7·47)	(−5·03, 28·05)	0·163	23·13*	48·04	77·07	22·93
	UK	68·88 (3·16)	(−12·11, 0·81)	0·083	11·73	21·95	66·34	33·66
	Algeria	34·73 (6·35)	(15·49, 41·50)	<0·001	87·90***		12·10	
	Mexico	45·67 (11·69)	(−5·28, 40·40)	0·125	56·61		87·81	12·19
	Pakistan	41·60 (7·35)	(4·35, 38·90)	0·017	25·96*	68·38	31·60	
	Netherlands	72·69 (5·75)	(−20·12, 1·20)	0·079	20·06		45·01	54·99***
	India	42·40 (4·69)	(11·64, 30·02)	<0·001	34·42***	73·64	93·64	6·36***
	Philippine	48·14 (3·55)	(7·25, 22·92)	0·001	11·20	61·20*	91·32	8·68**
	Romania	42·95 (5·25)	(9·26, 31·29)	0·001	80·72***		19·30	
	Hong Kong	53·90 (7·90)	(−8·08, 26·74)	0·278	32·02		68·00	
	Germany	68·53 (6·84)	(−-19·37, 8·77)	0·443	29·44		70·19	29·81
	Colombia	60·53 (9·88)	(−19·08, 24·48)	0·800	9·39		77·36	22·64
	Morocco	39·39 (7·25)	(8·77, 38·90)	0·003	55·90***	68·53***	31·50	
	Italy	63·12 (5·43)	(−10·52, 10·73)	0·984	8·07	24·55	72·49	27·51
	Iran	49·99 (6·87)	(−1·77, 28·23)	0·081	6·18	73·32**	87·94	12·06
	Lebanon	39·38 (8·18)	(6·89, 40·80)	0·008	29·97**	78·70**	21.30	
	Others	49·28 (1·57)	(10·58, 17·31)	<0·001	21·97***	54·45***	90·19	9·8%
	All (153 Countries)	51·09 (1·40)	(9·01, 15·27)	<0·001	18·91***	53·42***	86·66	13·34***

Note: Following the Statistics Canada guideline, some cells merged due to the low number of participants.

†Reference value; SE, standard error; CI, confidence interval. P-values: * P≤0·05; ** P≤0·01; *** P≤0·001.

3.4 S-25(OH)D concentration and VitD status by immigration status and season

The S-25(OH)D increased substantially during summer and fall compared with winter. Compared with January, the lowest weighted mean was found in February and the highest in September. The highest percentage of change (−37%) from the optimal level (75 nmol/L) was in February (Figure 1) and (Table A5, Appendix II). Non-immigrants had higher S-25(OH)D in all seasons, with significant increments in spring, summer, and fall compared with the winter season (Figure 2) and (Table A6, Appendix II).

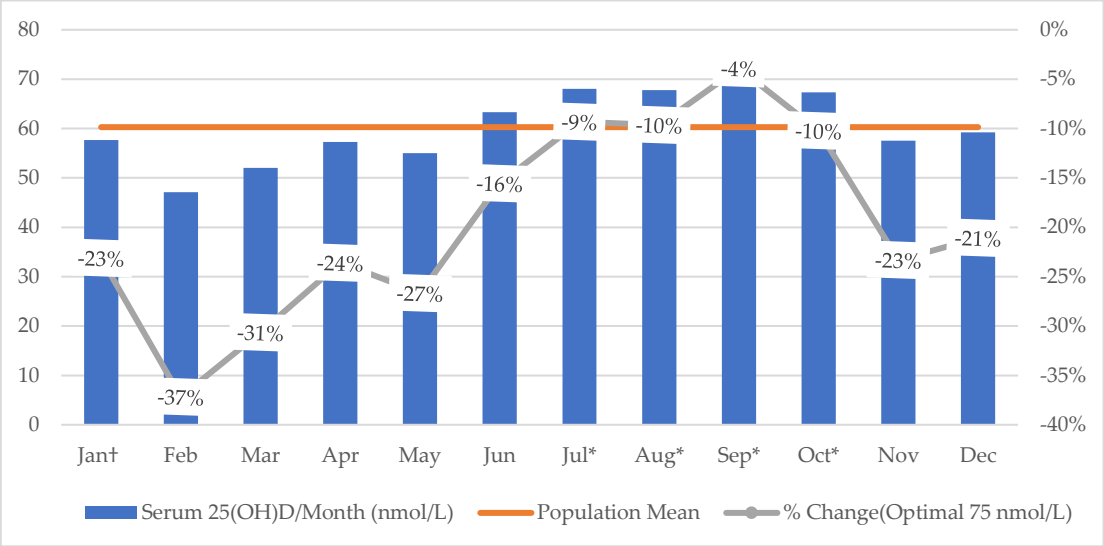


Fig. 1. Weighted mean S-25(OH)D (nmol/L)/month of test and percentage of change from the optimal level (75 nmol/L) using Cycles 3 and 4 of Canadian Health Measures Survey data (†Reference value *Significant at P≤0.05).

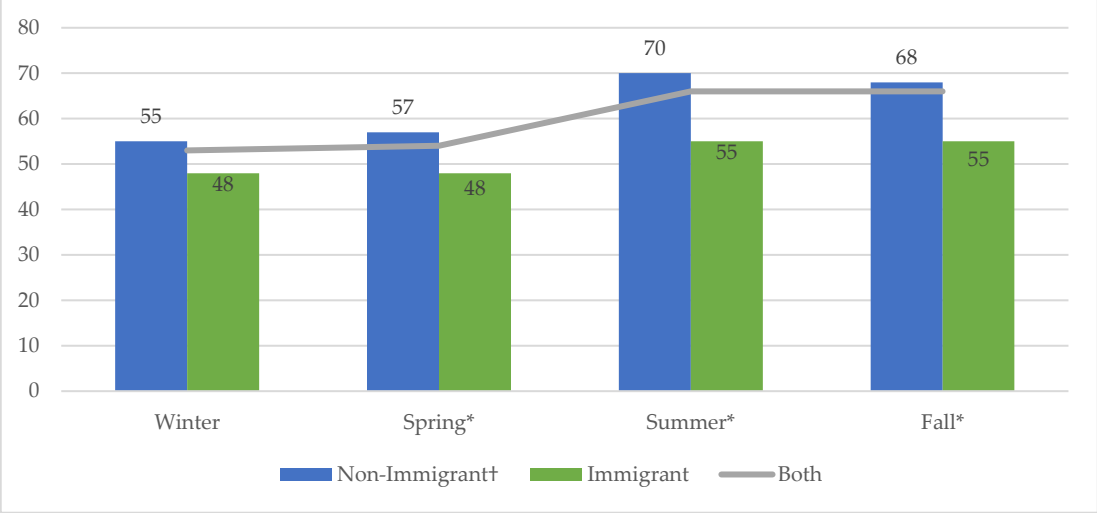


Fig. 2. Weighted seasonal variation in mean S-25(OH)D (nmol/L) based on immigration status using Cycles 3 and 4 of Canadian Health Measures Survey data († Reference value *Significant at P≤0.05).

3.5 Results of multivariate analysis

The final multi-linear regression model showed that immigrants had lower S-25(OH)D levels compared with non-immigrants (beta-estimate: −5.28, 95% CI: −7.48, −3.09, P<0.001) after adjusting for all covariates (Table 5). Ethnicity was the strongest predictor of S-25(OH)D in immigrants compared with non-immigrants. Other predictors such as consumption of dairy products (milk, cheese, and yogurt) and traveling to a sunny/warm climate in the two months before blood sampling were also strongly associated with differences in S-25(OH)D. Overall, the model showed a robust association between immigration status and concentrations of S-25(OH)D.

Table 5: Multivariate analysis-backward elimination method based on S-25(OH)D (nmol/L) and immigration status using Cycles 3 and 4 of Canadian Health Measures Survey data.

	S-25(OH)D		
	Beta estimate (SE)	**(95% CI)**	**P-value**
Immigration status	−5·28 (1·06)	−7·48, −3·09	<0·001
Sex	4·54 (0·88)	2·71, 6·36	<0·001
Season	3·44 (0·97)	1·42, 5·46	0·002
Age	0·14 (0·04)	0·07, 0·22	0·001
Traveled to a warm/sunny climate	6·31 (1·67)	2·85, 9·78	0·001
BMI	−4·89 (0·64)	−6·11, −3·48	<0·001
Dairy products (milk, cheese, yogurt)	5·79 (0·74)	4·25, 7·32	<0·001
Skin pigmentation (melanin)	1·36 (0·28)	0·79, 1·93	<0·001
Sunscreen use	4·95 (1·12)	2·63, 7·28	<0·001
Ethnicity	−15·11 (1·61)	−18·46, −11·78	<0·001
VitD-supplement and/or analog use	0·52 (0·16)	0·17, 0·86	0·005
-Const.	29·01 (5·91)	17·91, 40·12	<0·001

Adjusted linear regression for age, sex, income, education, BMI, season, sun exposure, sunscreen use, country of birth, melanin levels, ethnicity, vitD-medication/supplements, clothing type, and food consumption variables.

Significant at P≤0·05.

BMI, body mass index; SE, standard error; CI, confidence interval.

4. Discussion

This is the first national Canadian study to report vitD status among immigrants from different ethnic groups and origins compared with non-immigrants and has a global impact. A previous systematic review noted the need to assess vitD status and its determinants (including lifestyle factors) among subgroups living in the same country [35]. Moreover, research has highlighted the importance of comparing the same generation of immigrants rather than an aggregated generation [22], and gathering evidence, and formulating recommendations specific to sub-populations that may differ from the overall immigrant population [16].

The higher overall prevalence of vitD insufficiency among immigrants than non-immigrants in this study was consistent with global evidence suggesting that immigrants in Western countries have lower S-25(OH)D levels than non-immigrant populations [37 ,36 ,10 ,8] . Our multivariate analyses found ethnic background, having traveled to a sunny/warm climate, and low dairy product consumption were strong predictors of low S-25(OH)D levels among immigrants in Canada. Consistent with our findings, associations between S-25(OH)D levels and low income, winter season, low sunlight exposure, conservative dress, BMI (obesity), vitD supplements use, low physical activity, less traveling to a sunny/warm climate, non-white ethnicity, place of birth, and skin pigmentation were reported in previous studies [1, 10, 18].

While females are usually at higher risk for vitD deficiency [8, 36-38], females in our study had markedly higher S-25(OH)D levels than males. In 2015, Statistics Canada reported that females had more elevated serum vitD than males, more frequently using supplements than males (41% vs. 28%, respectively), and nearly 85% of vitD supplement users were above the cut-off (<50 nmol/L) compared with non-users (59%) [15]. McCormack et al. 2017, reported that females ≥ 19 years in Canada were using nutritional supplements (including vitD) more

than males [39]. However, the higher levels of S-25(OH)D could be partly explained by the finding that females used vitD supplements more than males (66% vs. 34%, P=0.019) (data not shown). In compliance with our finding, studies demonstrated that women who wear concealing clothes had lower S-25(OH)D levels than women dressed according to Western-style. It was well documented that the type of clothing determines the degree of sun exposure and supports/eliminates vitD's epidermal synthesis [8, 10, 18, 40, 41]. In this study, the effect of dress style on S-25(OH)D levels reduced (95% CI: -0.67, 15.82; P=0.070) in winter when both immigrants and non-immigrants wear winter clothes that cover all the body, while the difference remained statistically significant for spring, summer, and fall which may be due to different type of clothing during these seasons.

The current study found that immigrants with low household income were more linked with lower S-25(OH)D levels. A global vitD review reported that higher family income in developing countries was found inversely associated with hypovitaminosis D [10]. Other studies confirmed that lower-income immigrants were found with lower levels of S-25(OH)D than higher incomes [42, 43]. Consistent with our findings, global and Canadian vitD studies reported that obese adults had significantly lower S-25(OH)D than normal/underweight and overweight [1, 8, 15, 44]. Studies suggested that this may be due to vitD displacement in adipose tissue, which results in lower circulating S-25(OH)D levels in the blood [8].

Dairy products contain essential nutrients including vitD and calcium. Previous studies suggested insufficient consumption of these products was strongly associated with lower S-25(OH)D levels [10, 42, 45, 46]. Furthermore, milk in Canada is fortified with vitD, indicating a possibly magnified contribution of dairy products to serum vitD for both immigrant and non-immigrant consumers. Nonetheless, consumption of fortified milk and dairy products was

relatively higher in non-immigrants than immigrants, which may partially explain the difference in S-25(OH)D levels.

Canada regions have different weather conditions; nonetheless, it is expected that days in fall and winter are shorter than in summer and spring, with fewer hours of sunlight overall in Canada. In the present study, immigrants had less sun exposure than non-immigrants and had lower S-25(OH)D levels in winter than in summer. The seasonal variation in S-25(OH)D between immigrants and non-immigrants may be explained by the role of ultraviolet-B (UVB) light exposure in the endogenous synthesis of vitD. Previous studies also reported seasonal variations in vitD status [10, 19, 47]. Other studies reported the lowest levels of S-25(OH)D in winter [8, 48], which was consistent with our findings.

The non-sunscreen users had a higher prevalence of deficiency and insufficiency in vitD status than did the frequent sunscreen users. However, such difference could be partly explained by the fact that sunscreens are used as photoprotector as it minimizes ultraviolet-B (UVB) light exposure, hence lowers endogenous vitD activation, and thus increases the likelihood of developing vitD deficiency [49]. Nonetheless, in practice, sometimes the irregular use of sunscreen or inadequate amounts may not be enough to secure the body from all UVB light. Furthermore, sunscreen users might feel sunburn protected by blocking UVB light and, hence, tend to expose themselves more to the sun than non-users, increasing S-25(OH)D levels. In line with our finding, 25% of studies in a recent review concluded that sunscreen use was associated with higher S-25(OH)D concentration, while 10% of studies reported lower levels and 35% with no association [49, 50]).

Our data were obtained from immigrants from more than 150 countries, over 13 major ethnic groups, and therefore present a unique contribution to understanding Canada's ethnocultural

diversity concerning vitD status. Irrespective of the length of time living in Canada, immigrants who were born in Africa and Asia had lower S-25(OH)D levels than those born in North America. The lowest levels by country of birth were among immigrants born in Algeria, Lebanon, and Morocco. In terms of ethnic origins, the lowest S-25(OH)D levels were in Japanese, followed by Arab and Southeast Asian ethnic groups. Our adjusted linear regression model indicated ethnicity was the most important indicator of low S-25(OH)D levels among immigrants compared with non-immigrants. Similarly, previous research reported vitD deficiency was more common in people from specific racial backgrounds. For example, Asian (South Asia, Southeast), African, and Middle Eastern immigrant populations had lower S-25(OH)D than their counterparts in Western countries [8, 10, 48]. Middle Eastern immigrants (including Lebanese and Iranian people) were more frequently reported to have deficient/insufficient levels than other ethnic groups and non-immigrant populations in Western countries [10]. A systematic review of 112 studies (168,389 participants from 44 countries) reported insufficient levels in one-third of the included studies, with the highest levels among participants living in North America and lower levels among those living in the Middle East and African regions [35].

Dark-skinned individuals have a rich amount of melanin, which acts as a biological shield against UV radiation [8]. In the present study, skin pigmentation was used to rank participants based on melanin index values, where higher degrees of melanin indicated darker skin pigmentation. We found that immigrants had higher melanin levels than non-immigrants. Brook et al. reported the median 25(OH)D concentrations were higher in whites compared with non-whites in Canada [51] and several other studies have documented associations between skin pigmentation, ethnicity, geographical origins, and S-25(OH)D levels [8, 18, 52].

Research suggests that dark-skinned immigrants are at higher risk for vitD deficiency the longer time they spend in the host country [18] . In contrast, we found immigrants had markedly higher S-25(OH)D levels the longer they had lived in Canada after immigration. However, integration into a new life in Canada may reflect physical and behavioral adaptation to the surrounding environment, including lifestyle, diet, and climate changes. Immigration studies on acculturation and vitD found the length of time since immigration was a crucial indicator of lifestyle acculturation, and higher acculturation levels were associated with significantly higher S-25(OH)D levels [21, 53]. However, we found immigrants had less sun exposure and less frequent consumption of vitD-rich foods than non-immigrants, and the length of time since immigration reflected reasonable lifestyle acculturation in Canada. Moreover, genomic studies showed that vitD interacts and influences the human genome through vitD receptor-mediated gene regulation and drives evolution for genomic adaptations in the context of skin color lightening [54]. The biological adaptation process is part of micronutrient gene-regulation that supports vitD3 synthesis in regions with lower UVB radiation [54]. Therefore, epigenetic adaptations may partially explain why immigrants in Canada were prone to vitD deficiency in the short term after immigration, and levels of S-25(OH)D increased over time. Furthermore, our study showed that ethnic differences played a fundamental role in S-25(OH)D levels. Common genetic polymorphisms in the vitD receptor and vitD-binding protein may partly explain differences in vitD status between different ethnicities [55]. Therefore, vitD insufficiency and deficiency among immigrants may be associated with genetic variations combined with dietary and other environmental factors; this issue warrants further investigation.

To our knowledge, this was the first study assessing S-25(OH)D levels among Canadian immigrants different ethnic groups and origins compared with the non-immigrant population at the national level. The findings highlighted the need for further research investigating immigrants' health deterioration in the context of vitD. In addition, building knowledge of the relationship between health deterioration and vitD status along with similar biomarkers has important implications for responding to chronic and infectious diseases, including COVID-19.

Our study should be interpreted with consideration of its strengths and limitations. The CHMS data have many strengths. First, the CHMS provided the first national, comprehensive, and representative data for the Canadian population on vitD. Moreover, it used several clinical and laboratory measures to overcome the limitations of self-reported data [27]. Second, the study design and large sample size provided a nationally representative sample of immigrants in Canada. Third, it captured the ethnocultural diversity of immigrants from more than 150 countries and represented more than 13 major ethnic groups. Fourth, reported melanin level is a reliable indication of skin pigmentation. Fifth, S-25(OH)D levels were collected over the entire year, which enabled adjustment for seasonal variations in UVB light exposure, and offered a more accurate and representative measure of S-25(OH)D at the national level. Finally, the data were validated against other national data such as the Canadian Community Health Survey, Census data, and the 2011 National Household Survey [27]. However, immigrants were identified as landed people without detailed information about the immigration-specific status (e.g., refugees or asylum seekers) [27]. Research suggests refugees have a higher risk for vitD deficiency than other population groups [18, 19, 56, 57]. The lack of data on refugees and asylum seekers limited further subgroup analyses. Another limitation

of CHMS data is that the levels of biologically activated form 1,25(OH2)D was not measured in the study participants.

5. Conclusions

In conclusion, vitD deficiency is more common among Canadian immigrants than non-immigrants. Immigrants originating from African (Algeria and Morocco) and Asian (Lebanon) countries have a particularly low mean of S-25(OH)D. This study highlights ethnicity as a pivotal predictor of immigrants' lower S-25(OH)D levels; the Japanese, Arab, and Southeast Asian ethnic groups have a high prevalence of vitD deficiency. Short-term prevention strategies in community and clinical settings may be warranted, including vitD supplementation and awareness for people at higher risk. A long-term intervention plan may include developing/updating Canadian immigrant guidelines to incorporate evidence-based improvement strategies for vitD implementation.

Author Contributions:

SY and GW conceived the study. With close supervision from GW, SY managed the data, verified the analytical methods, and prepared the tables and figures. AH verified the underlying data at the Research Data Center. SY and MF interpreted the results and prepared the final draft. All authors including DM, IC, and MP contributed to the design and analysis of the research, and the substantive review of the manuscript.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement:

All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025). The CHMS was approved by the Health Canada Research Ethics Board.

Informed Consent Statement:

Written consents were collected by Statistics Canada from all participants for a personal interview, physical measures, and biospecimens collection.

Data Availability Statement:

Data described in the manuscript, codebook, and analytic code will not be made publicly available because the data are confidential national survey data hosted by Statistics Canada.

Acknowledgments:

The authors acknowledge the team from the Carleton, Ottawa, Outaouais Local Research Data Centre for assistance with access to CHMS data. CHMS data were obtained and supported by funding to the Canadian Research Data Centre Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. Although the research and analysis were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Conflicts of Interest:

The authors declare no personal or financial conflicts of interest.

References (main manuscript 3.1)

1. Charoenngam, N., A. Shirvani, and M.F. Holick, *Vitamin D for skeletal and non-skeletal health: What we should know.* Journal of clinical orthopaedics and trauma, 2019. **10**(6): p. 1082-1093.
2. Shin, S.Y., et al., *Measurement of Serum Total Vitamin D (25-OH) Using Automated Immunoassay in Comparision With Liquid Chromatography Tandem-Mass Spectrometry.* Journal of clinical laboratory analysis, 2013. **27**(4): p. 284-289.
3. Atef, S.H., *Vitamin D assays in clinical laboratory: past, present and future challenges.* The Journal of steroid biochemistry and molecular biology, 2018. **175**: p. 136-137.
4. Martens, *Immunoassay for free vitamin D*. 2018.
5. Nowson, C.A., et al., *Vitamin D and health in adults in Australia and New Zealand: a position statement.* Medical Journal of Australia, 2012. **196**(11): p. 686-687.
6. Heaney, R.P., et al., *Vitamin D3 is more potent than vitamin D2 in humans.* The Journal of Clinical Endocrinology & Metabolism, 2011. **96**(3): p. E447-E452.
7. De Boer, I.H., et al., *25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification.* Journal of the American Society of Nephrology, 2009. **20**(8): p. 1805-1812.
8. Spiro, A. and J. Buttriss, *Vitamin D: an overview of vitamin D status and intake in E urope.* Nutrition bulletin, 2014. **39**(4): p. 322-350.
9. Zmijewski, M.A., *Vitamin D and human health*. 2019, Multidisciplinary Digital Publishing Institute.
10. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D.* Osteoporosis international, 2009. **20**(11): p. 1807-1820.
11. Ross, A., et al., *Dietary reference intakes: calcium and vitamin D. Committee to review dietary reference intakes for vitamin D and calcium food and nutrition board. Washington, DC: National Academy of Sciences; 2011*. 2011.
12. Vieth, R., *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml).* Best practice & research Clinical endocrinology & metabolism, 2011. **25**(4): p. 681-691.
13. Dawson-Hughes, B., *Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment.* UpToDate [Online].[cited Feb 2021], 2014.
14. Pham, T., *Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal.* 2012.
15. Janz, T. and C. Pearson, *Vitamin D blood levels of Canadians*. 2013: Statistics Canada Ottawa (Canada).

16. Yousef, S., et al., *Study protocol: worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations—a systematic review and meta-analysis.* Systematic reviews, 2019. **8**(1): p. 1-6.
17. Cashman, K.D., et al., *Vitamin D deficiency in Europe: pandemic?* The American journal of clinical nutrition, 2016. **103**(4): p. 1033-1044.
18. Martin, C.A., U. Gowda, and A.M. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**(1): p. 21-32.
19. Eggemoen, Å.R., et al., *Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults.* BMJ open, 2013. **3**(10): p. e003293.
20. Chui, T., *Statistics Canada. Immigration and ethnocultural diversity in Canada: national household survey. Ottawa: Statistics Canada*. 2011.
21. Salant, T. and D.S. Lauderdale, *Measuring culture: a critical review of acculturation and health in Asian immigrant populations.* Social science & medicine, 2003. **57**(1): p. 71-90.
22. Zhu, L., *Depression risks and correlates among different generations of Chinese Americans: the effects of relationships with friends and relatives.* Social Sciences, 2017. **6**(2): p. 56.
23. Stephens, W., et al., *Observations on the natural history of vitamin D deficiency amongst Asian immigrants.* QJM: An International Journal of Medicine, 1982. **51**(2): p. 171-188.
24. Stern, P.J., *Generational differences.* Journal of Hand Surgery, 2002. **27**(2): p. 187-194.
25. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Bulletin of the World Health Organization, 2007. **85**: p. 867-872.
26. Day, B., et al., *Canadian Health Measures Survey: ethical, legal and social issues.* Health Reports, 2007. **18**: p. 37-51.
27. Ng, E., *Canadian Health Measures Survey: A tool for immigrant health research?* Health Reports, 2015. **26**(3): p. 3.
28. StatisticsCanada. *Canadian Health Measures Survey, Cycle 4, 2014-2015 - Privacy impact assessment summary*. 2021; Available from: https://www.statcan.gc.ca/eng/about/pia/chmsc4.
29. StatisticsCanada. *2012-2013 Canadian Health Measures Survey, Cycle 3 - Privacy impact assessment*. 2021; Available from: https://www.statcan.gc.ca/eng/about/pia/chmsc3.

30. HealthCanada, *Canadian Guidelines for Body Weight Classification in Adults - Quick Reference Tool for Professionals*. 2003.
31. Onis, M.d., et al., *Development of a WHO growth reference for school-aged children and adolescents.* Bulletin of the World Health Organization, 2007. **85**: p. 660-667.
32. CanadianPhysicalActivity, *Sedentary Behaviour Guidelines.* Canadian Society for Exercise Physiology, 2012.
33. StatisticsCanada, *Canadian Health Measures Survey (CHMS)Data User Guide: Cycle 3*. 2015.
34. StatisticsCanada. *Canadian Health Measures Survey (CHMS)- Cycle 4*. 2014; Available from: https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=148760.
35. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British journal of nutrition, 2014. **111**(1): p. 23-45.
36. Pludowski, P., et al., *Vitamin D status in central Europe.* International Journal of Endocrinology, 2014. **2014**.
37. Lips, P., *Vitamin D status and nutrition in Europe and Asia.* The Journal of steroid biochemistry and molecular biology, 2007. **103**(3-5): p. 620-625.
38. Alshahrani, A.A., *Vitamin D deficiency and possible risk factors among Middle Eastern university students in London, Ontario, Canada.* 2014.
39. McCormack, D., X. Mai, and Y. Chen, *Determinants of vitamin D supplement use in Canadians.* Public Health Nutrition, 2017. **20**(10): p. 1768-1774.
40. Knoss, R., L.G. Halsey, and S. Reeves, *Ethnic dress, vitamin D intake, and calcaneal bone health in young women in the United Kingdom.* Journal of Clinical Densitometry, 2012. **15**(2): p. 250-254.
41. Ojah, R.C. and J.M. Welch, *Vitamin D and musculoskeletal status in Nova Scotian women who wear concealing clothing.* Nutrients, 2012. **4**(5): p. 399-412.
42. Mark, S., *Vitamin D status and recommendations to improve vitamin D status in Canadian youth.* 2010.
43. Naugler, C., et al., *Association of vitamin D status with socio-demographic factors in Calgary, Alberta: an ecological study using Census Canada data.* BMC public health, 2013. **13**(1): p. 1-10.
44. Ghasemian, R., et al., *The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis.* MedRxiv, 2020.
45. Munasinghe, L.L., et al., *Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010.* British journal of nutrition, 2017. **117**(3): p. 457-465.

46. Wang, L., et al., *Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women.* Hypertension, 2008. **51**(4): p. 1073-1079.
47. Thuesen, B., et al., *Determinants of vitamin D status in a general population of Danish adults.* Bone, 2012. **50**(3): p. 605-610.
48. Renzaho, A.M., J.A. Halliday, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review.* Nutrition, 2011. **27**(9): p. 868-879.
49. Neale, R., et al., *The effect of sunscreen on vitamin D: a review.* British Journal of Dermatology, 2019. **181**(5): p. 907-915.
50. Young, A., et al., *Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn.* British Journal of Dermatology, 2019. **181**(5): p. 1052-1062.
51. Brooks, S.P., et al., *An analysis of factors associated with 25-hydroxyvitamin D levels in white and non-white Canadians.* Journal of AOAC International, 2017. **100**(5): p. 1345-1354.
52. Nimitphong, H. and M.F. Holick, *Vitamin D status and sun exposure in Southeast Asia.* Dermato-endocrinology, 2013. **5**(1): p. 34-37.
53. Sanou, D., et al., *Acculturation and nutritional health of immigrants in Canada: a scoping review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.
54. Carlberg, C., *Nutrigenomics of vitamin D.* Nutrients, 2019. **11**(3): p. 676.
55. Leandro, A., et al., *Genetic polymorphisms in vitamin D receptor, vitamin D-binding protein, Toll-like receptor 2, nitric oxide synthase 2, and interferon-γ genes and its association with susceptibility to tuberculosis.* Brazilian Journal of Medical and Biological Research, 2009. **42**: p. 312-322.
56. Aucoin, M., et al., *Vitamin D status of refugees arriving in Canada: findings from the Calgary Refugee Health Program.* Canadian Family Physician, 2013. **59**(4): p. e188-e194.
57. Baauw, A., et al., *Health needs of refugee children identified on arrival in reception countries: A systematic review and meta-analysis.* BMJ paediatrics open, 2019. **3**(1).

Supporting material

Appendix I: Supporting information regarding the steps used to combine Cycles 3 and 4, and detailed information about the calculation of the variables of interest (Table A1).

Appendix I.1. Combining Cycles 3 and 4

The CHMS is the first national population-based survey on vitamin D (vitD) conducted in Canada. Data were collected in six cycles biannually between 2007–2019. Compared with other cycles, Cycle 3 (2012–2013) and Cycle 4 (2014–2015) are considered the most thematically consistent in terms of vitD-related sociodemographic characteristics, lifestyle factors, vitD-rich foods consumption, and behavioral, environmental, and biological determinants. Immigrant status was defined as being born outside Canada [1]. In this study, we combined data from Cycles 3 and 4 to increase the sample size and provide a more stable and precise estimate of sampling variability at the national level than was possible using a single data cycle estimate. The combination of the two cycles followed Statistics Canada's guideline for combining CHMS cycles. As recommended, we used bootstrap 1–bootstrap 500, full-weight or applicable weight, and the required degrees of freedom to correct variance estimations. Therefore, the pre-specified combined full-sample weights and degrees of freedom for the two cycles were used in our analyses. The single-cycle weight was dropped from the dataset as it was a cycle-specific weight. The combined response rate (response rate for all study components, such as household visit, blood samples, and activity monitor) at the Canadian level for cycle 3 was 51.7%, and that for cycle 4 was 53.7% [2, 3].

Appendix I.2. Population, Comparators, Measures, and Outcome

The population of interest in this study was first-generation Canadian immigrants (foreign-born) from different origins and ethnicities. The comparators were non-immigrants (native-

born population) and the white ethnic grouping. The S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd, Stillwater, Minnesota, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. The inter-assay Coefficients of Variation for the S-25(OH)D was 13.0% and the precision for <20 nmol/L, 20-100 nmol/L and >100 nmol/L levels were 15.0%, 10.0% and 12.0%, respectively[4].

The results are presented as weighted means or proportions only. The weighted results and proportions were based on the total number of 11,579 participants. The number of participants for each group cannot be published because of Statistics Canada's restrictions policy relates to publishing weighted results. The weighting technique for complex survey results refers to statistical adjustments that have been used to correct and improve the accuracy of the survey estimates. The survey weights adjust for unequal probabilities of selection that often have occurred during sampling design and to help compensate for survey non-response weights. Thus, by using the survey weights to create estimates should yield approximately unbiased national prevalence estimates and reduce non-response bias that can be introduced due to random missing values. The study outcomes were the S-25(OH)D levels and vitD status.

Appendix I.3. Variables of Interest

The data manipulation and all derived variables were consistent with Statistics Canada's instructions based on the specific cycle user guide, data codebook, instructions for combining more than one cycle, and the derived variable specifications[2] **.** The CHMS microdata are hosted in secure centers overall in Canada. These data were accessed and analyzed at the Carleton, Ottawa, Outaouais Local Research Data Centre (COOLRDC), located in the Morisset Library at the University of Ottawa.

Appendix II: Supporting information including (Tables A2-A6) and (Figures A1-A2).

This Appendix sets out the steps followed in combining Cycles 3 and 4 of the Canadian Health Measures Survey (CHMS), variables of interest, critical data manipulation stages, and other methodological aspects. This Appendix contains supplementary material for the manuscript entitled “Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study using the Canadian Health Measures Survey.”

Table A1. Variables of interest in Cycles 3 and 4 of the Canadian Health Measures Survey

Variable	Description
Dependent variable	We used the contentious variable S-25(OH)D (mmol/L). We categorized vitD status using the following cut-offs for S-25(OH)D: (<30 (nmol/L); (<50 (nmol/L); (<75 (nmol/L); and (≥75 (nmol/L). First, <30 nmol/L is used to identify deficient people. Second, (<50 nmol/L) is a cut-off for the insufficient 25(OH) D, which includes the deficient and insufficient people (it is an accumulating value and not range for the insufficient people). Third, (<75 nmol/L) is a cut-off and accumulating value for deficient, insufficient, and sufficient. Fourth (≥75 (nmol/L), it is the "no added value" or the "optimal" as defined by IOM or other experts [5-7]. Moreover, we used ranges of S-25(OH)D for the above mentioned cut-offs (<30 nmol/L; 30-49 nmol/L; 50-74 nmol/L and ≥75 nmol/L) for sub-groups of participants.
Independent variables	
Immigration status	Landed immigrant (Yes, No).
Age at time of immigration	Age at immigration was categorized as <18 years or ≥18 years.
Time since immigration	We used the continuous variable "length of time since first came to live in Canada" to categorize time since imigration at two cutoff points (≤5 years and >5 years; ≤10 years and >10 years). We used these points as indications of recent immigrants and long-term immigrants.
Sex	Male/Female.
Age	Contentious and categorical variables.
Education	Education was classified as ≤secondary school or >secondary school.
Household income	Household income was derived and imputed by Statistics Canada. The contentious variable and categorical variables (<50000, 50000–100000, and >100000) were used as appropriate.
Body mass index	Calculated as weight divided by height squared (kg/m^2). We used body mass index norms for adults (≥18 years) based on national standards for weight classification [8]. For children (3–17 years), body mass index was classified according to World Health Organization percentiles [9].
Smoking	We categorized smoking status into two groups (former/non-smoker vs. current smoker).
Alcohol	We categorized alcohol consumption into two groups (former/non-drinker vs. current drinker).
Vitamin D-containing supplements/medications	All prescription medications, over-the-counter, and herbal remedies taken in the past month (including vitD supplements and medications) were recorded in the CHMS data. The Anatomical Therapeutic Chemicals (ATCs) is a system that classifies products according to the organ and their chemical, pharmacological, and therapeutic properties. The vitD -related ATC codes were selected (A11CC01–05). These ATC codes represent ergocalciferol (vitD 2), dihydrotachysterol (synthetic vitD analog), alfacalcidol (analog of vitD), calcitriol, and cholecalciferol (vitD 3). Users

	of any of these were recorded as “yes,” non-users as “no,” and not respondents as “missing.”
Dietary intake	The CHMS collected dietary intake of different types of each item (red meat, liver, fish, egg, milk, cheese, yogurt, margarine) based on the previous month’s consumption. Statistics Canada prepared derived variables for each item to describe the number of times that item had been consumed/year. These derived variables were used to calculate consumption per week or day as needed. Different types of each item were merged into a single category. For example, all kinds of milk (plain, flavored, omega-3) were merged as “all milk.” The same procedure was used for “all meats” (e.g., red meat, liver, sausage, hotdog), as well as “all cheese,” “all yogurt,” “all eggs,” and “all margarine.” Another category was used for all dairy products, called “all diary.” We also used fish consumption in the past 2 months as (Yes vs. No). Values of ≤1 time/week vs. >1 time/week were used for all categories, except all milk and all dairy, which used ≤7 times/week vs. >7 times/week.
Calcium and phosphorus	Contentious variables (mmol/L).
Pregnancy	Pregnancy was classified as Yes or No.
Ethnicity	Broadly, ethnicity was classified into two main groupings as white or non-white. Statistics Canada categorized non-white into the 12 largest ethnic groups (Aboriginal, South Asian, Chinese, Black, Filipino, Latin American, Arab, South East Asian, West Asian, Korean, Japanese, Multiple ethnicities), and another category for all other ethnicities.
Season of blood sampling	The season variable was created based on the derived variable of “month of blood sampling.” We categorized the season as winter (December–February), spring (March–May), summer (June–August), and fall (September–November).
Regions of birth	We used five regions: Canada and North America; South and Central America and the Caribbean; Europe; Africa; and Asia.
Countries of birth	We used the geographic classifications of Statistics Canada to identify the country of birth for all CHMS participants (153 countries)[10]. We ranked and selected the top 20 countries based on the number of participants (≥30 participants from each). These countries were Canada, China, the US, France, Jamaica, the UK, Algeria, Mexico, Pakistan, the Netherlands, India, the Philippines, Romania, Hong Kong, Germany, Colombia, Morocco, Italy, Iran, and Lebanon. We combined all other countries in one category, “Other,” and combined the 153 countries (excluding Canada) in another class to represent all foreign-born immigrants.
Sun exposure (10 am to 4 pm)	Sun exposure was classified as <30 minutes\day or ≥30 minutes\day.
Sunscreen application	Sunscreen application was classified as Yes or No.
Clothing type	The clothing type was based on coverage and classified as Yes or No. Yes indicated typically covered (face, ears, neck or arms and legs).

Physical activity	Physical activity for adults (≥18 years) was calculated based on the Canadian Physical Activity Guidelines (CPAG). The CPAG recommendation for adults is to accumulate at least 150 minutes of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of ≥10 minutes. The CPAG recommendation for children (5–17 years) is to accumulate at least 60 minutes of moderate-to-vigorous intensity physical activity daily for at least three days per week [11].
Traveled to a sunny/warmer place (in the past two months)	Travelling to a sunny/warmer place in the past two months was classified as Yes or No.
Skin pigmentation (melanin levels)	Melanin is the component that gives skin its natural color. Melanin levels were measured from the back of the hand three times; a fourth measurement was required if the difference between the first three melanin values deviated by more than 10 units. The final average calculated by Statistics Canada indicates the absolute index values of melanin, where the higher the value, the more melanin present in the epidermal. The device used for measurement was the DSM II ColorMeter (Cortex Technology, Hadsund, Denmark).

S-25(OH)D: Serum 25-hydroxyvitamin D

Appendix II: Supporting information (Tables A2-A6 and Fig.A1-Fig. A2).

Table A2: Weighted prevalence and mean S-25(OH)D (nmol/L) levels and basic study characteristics using Cycles 3 and 4 of Canadian Health Measures Survey data

		Cycle 3 (49.52%) %	Cycle 4 (50.48%) %	Total (100%) %
Immigration status	Immigrant	24·5	19·38	21·90
Ethnic group	White	75·10	78·87	76·98
Sex	Female	50·00	50·10	50·08
Age (years)	<5	2·47	2·14	2·30
	5–11	7·92	8·17	8·04
	12–17	7·58	7·21	7·39
	18–64	70·70	70·29	70·54
	>64	11·20	12·20	11·72
Household income (CAD)	<50000	38·10	32·91	35·45
	50000–100000	36·00	37·26	36·61
	>100000	26·00	29·84	27·93
S-25(OH)D (nmol/l)	<50	34·96	37·73	36·36
Weighted Mean		**Mean (SE)**	**Mean (SE)**	**Mean (SE)**
	Age (years)	39·08 (0·15)	39·35 (0·09)	39·23 (0·085)
	S-25(OH)D (nmol/L)	61·29 (2·78)	59·16 (1·99)	60·28 (1·69)

SE, standard error.

Table A3: Weighted prevalence of vitamin D-rich food/fish consumption for immigrants and non-immigrants using Cycles 3 and 4 of Canadian Health Measures Survey data

		Non-Immigrants (78.9%), %	Immigrants (21.9%), %	All participants (100%), %	P-value
All meats (red meat, liver, hotdog, and sausage)	>1 time/week	90·47	78·72	87·89	<0·001
All eggs (yolk/omega-3)	>1 time/week	59·68	66·95	61·26	0·067
All milk (plain, flavored, and omega-3)	>7 times/week	54·63	48·38	53·27	0·027
All cheese (cottage and other)	>1 time/week	86·70	63·26	81·57	<0·001
All yogurt	>1 time/week	72·19	70·15	71·75	0·577
All dairy products (milk, yogurt, and cheese)	>7 times/week	83·38	75·38	81·64	<0·001
All margarine (plain and omega-3)	>1 time/week	84·11	70·95	81·90	0·007
Fortified juice with calcium/vitamin D	>1 time/week	7·01	6·12	6·81	0·452
Fish consumption/past 2 months	Yes (No[†])	25·18	17·09	23·43	0·046

Reference values: ≤1 time/week; ≤7 times/week.

[†]Reference value; P-values: ≤0·05

Table A4: Weighted means for S-25(OH)D (nmol/L) and vitamin D status by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures

		S-25(OH)D (nmol/L)			S-25(OH)D status			
		Mean (SE)	**(95% CI)**	**P-value**	**<30(nmol/L (10.3%), %**	**<50(nmol/L (36.4%), %**	**<75(nmol/L (76.1%), %**	**≥75(nmol/L (23.9%), %**
Household income (CAD)	<50000†	56·18 (1·90)	-		13·95	45·10	79·43	20·57
	50000–100000	61·44 (1·81)	(−7·73, −2·79)	<0·001	9·67	33·14	76·02	23·98
	>100000	63·66 (1·79)	(−9·97, −4·98)	<0·001	6·53***	29·64***	72·09	27·91**
Education	≤Secondary school†	59·41 (1·64)			9·57	36·81	77·58	22·42
	>Secondary school	61·00 (1·86)	(−3·59, 0·41)	0·113	10·87	35·83	74·97	25·03
Pregnancy	No†	60·35 (2·15)	-		11·72	36·88	75·29	24·71
	Yes	51·22 (7·40)	(−6·69, 24·94)	0·244	2·11	45·70	93·21	6·79*
Smoking habits	Former/non-smoker†	61·59 (1·66)	-		9·98	34·12	73·82	26·18
	Current smoker	53·09 (2·12)	(5·74, 11·24)	<0·001	14·88*	50·71***	85·02	14·98***
Alcoholic beverages	Former/non-drinker†	54·25 (2·17)	-		15·72	38·15	81·44	18·56
	Current drinker	61·33 (1·67)	(−10·49, 3·66)	<0·001	9·73**	34·70***	74·70	25·30**
Meet the physical activity recommendation	No†	58·79 (1·54)	-		11·32	39·34	77·91	22·09
	Yes	63·80 (2·34)	(−8·26, 1·76)	0·004	8·01	29·54***	72·86	27·14*
Clothing	Uncovered†	62·07 (1·69)	-		8·23	31·13	74·85	25·15
	Typically covered	57·91 (2·00)	(1·46, 6·85)	0·004	12·86**	42·58***	77·86	22·14

† Reference value; SE, standard error; CI, confidence interval; BMI, body mass index.

P-values: * $P \leq 0{\cdot}05$; ** $P \leq 0{\cdot}01$; *** $P \leq 0{\cdot}001$

Table A5: Weighted means for S-25(OH)D (nmol/L) by season and month of blood test using Cycles 3 and 4 of Canadian Health Measures Survey data

		S-25(OH)D (nmol/L)		
		Mean (SE)	**(95% CI)**	**P-value**
Season	Winter†	53·80 (2·47)	-	
	Spring	54·63 (1·41)	(−7·16, 5·49)	0·786
	Summer	66·13 (2·38)	(−18·50, −6·16)	<0·001
	Fall	66·00 (3·63)	(−20·59, −3·83)	0·006
Month	January†	57·67 (9·25)	-	
	February	47·13 (6·17)	(−25·73, 4·65)	0·164
	March	52·02 (9·57)	(−28·63, 18·86)	0·674
	April	57.31 (1.64)	(−23·46, 3·10)	0·126
	May	55·00 (2·17)	(−21·38, 5·63)	0·240
	June	63·34 (8·61)	(−38·14, 5·73)	0·140
	July	68·02 (5·41)	(−37·88, −3·89)	0·018
	August	67·78 (7·31)	(−40·77, −0·53)	0·045
	September	72·08 (10·24)	(−49·86, −0·04)	0·050
	October	67·34 (5·39)	(−37·99, −2·42)	0·028
	November	57·52 (2·80)	(−24·80, −4·02)	0·149
	December	59·20 (13·18)	(−42·89, 18·75)	0·425

†Reference value; SE, standard error; CI, confidence interval; P-values: ≤0·05

Table A6: Weighted mean S-25(OH)D concentrations (nmol/L) by immigration status and season using Cycles 3 and 4 of Canadian Health Measures Survey data

		Non-Immigrant †	Immigrant		
		Mean (SE)	**Mean (SE)**	**(95% CI)**	**P-value**
Season	**Winter**	55·36 (2·33)	47·79 (4·55)	(−0·67, 15·82)	0.070
	Spring	56·94 (1·62)	47·71 (3·07)	(2·27, 16·19)	0·012
	Summer	70·03 (2·23)	55·21 (1·76)	(9·28, 20·36)	<0·001
	Fall	68·11 (3·55)	54·87 (3·95)	(8·00, 18·47)	<0·001

†Reference value; SE, standard error; CI, confidence interval; P-values: ≤0·05

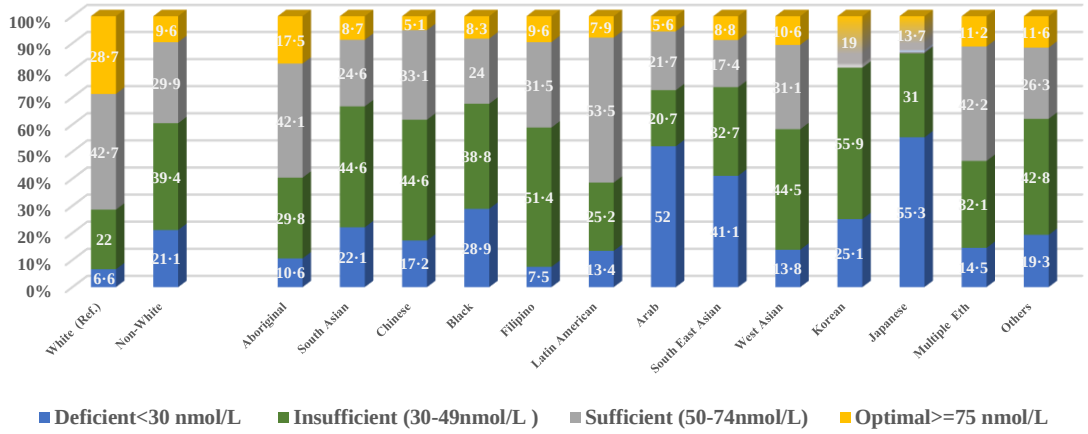


Figure A1: Weighted prevalence of S-25(OH)D status for immigrants from different ethnic groups using Cycles 3 and 4 of Canadian Health Measures Survey data.

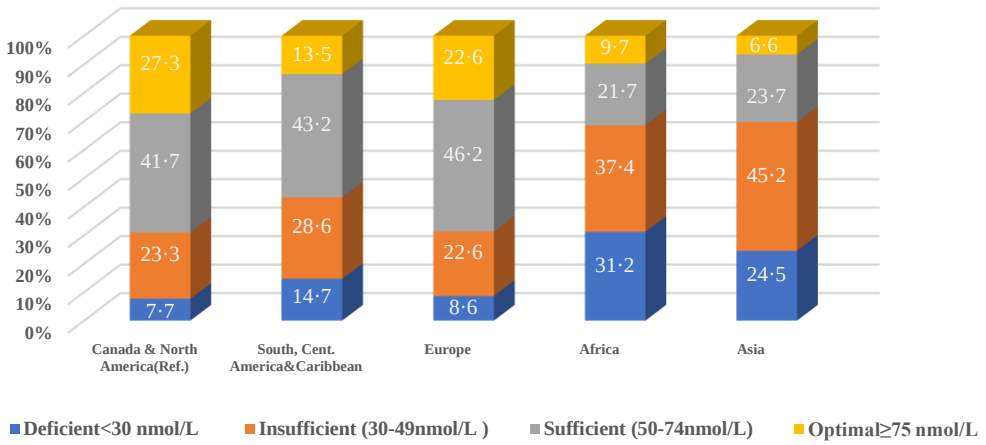


Figure A2: Weighted prevalence of S-25(OH)D status for immigrants by region of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

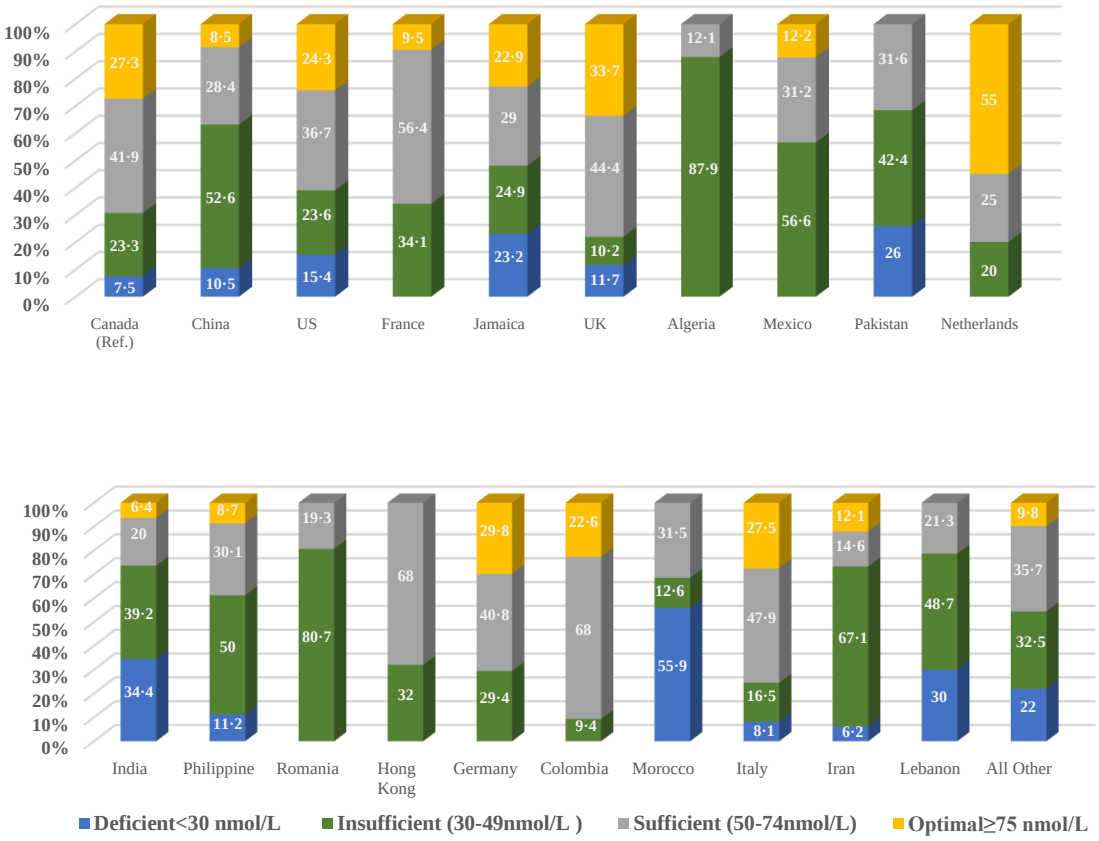


Figure A3: Weighted prevalence of S-25(OH)D status by country of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

References

1. Ng, E., *Canadian Health Measures Survey: A tool for immigrant health research?* Health Reports, 2015. **26**(3): p. 3.
2. StatisticsCanada, *Canadian Health Measures Survey (CHMS)Data User Guide: Cycle 3*. 2015.
3. StatisticsCanada. *Canadian Health Measures Survey (CHMS)- Cycle 4*. 2014; Available from: https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=148760.
4. Munasinghe, L.L., et al., *Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010.* British journal of nutrition, 2017. **117**(3): p. 457-465.
5. Ross, A., et al., *Dietary reference intakes: calcium and vitamin D. Committee to review dietary reference intakes for vitamin D and calcium food and nutrition board. Washington, DC: National Academy of Sciences; 2011*. 2011.
6. Vieth, R., *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml).* Best practice & research Clinical endocrinology & metabolism, 2011. **25**(4): p. 681-691.
7. Dawson-Hughes, B., *Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment.* UpToDate [Online].[cited Feb 2021], 2014.
8. HealthCanada, *Canadian Guidelines for Body Weight Classification in Adults - Quick Reference Tool for Professionals*. 2003.
9. Onis, M.d., et al., *Development of a WHO growth reference for school-aged children and adolescents.* Bulletin of the World Health Organization, 2007. **85**: p. 660-667.
10. Statistics, C. *Standard classification of countries and areas of interest (SCCAI)*. 2017; Available from: https://publications.gc.ca/site/eng/9.856211/publication.html.
11. CanadianPhysicalActivity, *Sedentary Behaviour Guidelines.* Canadian Society for Exercise Physiology, 2012.

3.2 Melanin levels and vitamin D among first-generation immigrants from different ethnic groups and origins

Section overview

Melanin levels were measured as part of CHMS data for all participants using DSM II ColorMeter. Melanin was measured from the back of the hand three times; a fourth measurement was required if the difference between the first three melanin values deviated by more than 10 units. The higher the final average indicates the more melanin is present in the epidermal and the darker the person's skin. No previous study has examined the relationship between melanin levels and S-25(OH)D among immigrants based on their ethnicity and region/country of birth compared with non-immigrants. This study explored the associations between melanin levels and participants' sociodemographic characteristics, use of indoor tanning, and clarified whether melanin levels explained the variations in vitamin D between immigrants compared with native-born Canadians.

Immigrants had higher melanin levels (darker skin) compared with non-immigrants, but there was no difference in melanin by their length of stay in Canada. Melanin levels were positively weakly correlated with S-25(OH)D. This finding contradicted the existing knowledge of negative correlation between melanin levels and with S-25(OH)D. Melanin was not associated or correlated with the use of indoor tanning equipment or the frequency of use.

Although the relationship between the two outcomes (vitamin D and melanin) is well established in the literature, this relationship has not been fully elucidated in the context of first-generation immigrants and inherent factors related to these immigrants. Therefore, the

present study was designed to fill this knowledge gap and explored whether melanin levels explained S-25(OH)D variations between immigrants and native-born Canadians.

Manuscript status

This manuscript has been published: *Frontiers in Medicine, Accepted December 16, 2022; doi:10.3389/fmed.2022.992554 (In press 2022).*

Yousef S*, Papadimitropoulos M, Faris M, Hasan H, Hossain A, Colman I, Manuel D, Wells G.A.

Author roles and contributions

SY and GW conceived the study. With close supervision from GW, SY managed the data, verified the analytical methods, and prepared the tables and figures. AH verified the underlying data at the Research Data Center. SY, MF, and HH interpreted the results. SY prepared the final draft. All authors including IC, MP, DM, AH, MF, and HH contributed to the design and analysis of the research, and substantive review of the manuscript.

Related thesis appendices

Appendix A3:

The PDF of the published manuscript (In press) is presented in Appendix A3.2.

Melanin levels in relation to vitamin D among first-generation immigrants from different ethnic groups and origins: A comparative national Canadian cross-sectional study

Said Yousef*; Manny Papadimitropoulos; MoezAlIslam Faris; Hayder Hasan; Alomgir Hossain; Ian Colman; Douglas Manuel; George A Wells

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

Hayder Hasan, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Douglas Manuel, MD, MSc.

Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Introduction: Immigrants to Western countries tend to have darker skin than native-born populations. We examined the relationship between skin melanin and serum vitamin D (S-25(OH)D) levels and explored whether melanin levels explained S-25(OH)D variations between immigrants and native-born Canadians. This study offers novel findings as no such study has been conducted.

Methods: We used a national cross-sectional population-based design with data from the Canadian Health Measures Survey. Skin melanin levels among first-generation immigrants based on their ethnicity and origin/country of birth were compared with white and native-born populations. We assessed the association between S-25(OH)D and melanin after adjusting for independent variables related to S-25(OH)D, melanin level, and immigration status.

Results: Of 11,579 participants, 21.9% were immigrants aged 3–79 years (mean age 39.23 years). Compared with non-immigrants, immigrants had lower S-25(OH)D levels (mean: 51.23 *vs*. 62.72; 95%CI: 8.37, 14.62; $P<0.001$) but higher melanin levels (mean [*SE*]: 17.08 [0.25] *vs*. 16.29 [0.29]; 95%*CI*: −1.29, −0.281; $P=0.004$). Melanin did not differ by length of stay in Canada but was weakly positively correlated ($r=0.088$, $P<0.001$) with S-25(OH)D. Sex (male), age (≥18 years), summer/fall seasons, sunlight exposure, sunscreen non-use, smoking, and alcohol consumption were associated with higher melanin levels, whereas indoor tanning use was not.

Conclusion: Skin melanin levels were associated with sociodemographic and behavioral characteristics. Immigrants had higher melanin levels, but melanin did not differ by length of stay in Canada. The weak positive correlation between melanin and S-25(OH)D suggested

confounding factors may impact the relationship between melanin levels, S-25(OH)D, and immigration status.

Keywords: melanin; serum vitamin D; 25-hydroxyvitamin D; 25(OH)D; immigrants' origins and ethnicities; indoor tanning

Key Messages

- Immigrants to Western countries have higher melanin (darker skin) and lower S-25(OH)D levels than native-born populations, but it remains unclear if melanin levels explain variations in S-25(OH)D between first-generation immigrants (based on ethnicity/country of birth) and native-born populations.
- We used national Canadian data that captured the ethnocultural diversity of immigrants from more than 150 countries and over 13 major ethnic groups to investigate whether melanin levels explained variations in S-25(OH)D between immigrants and native-born populations.
- Immigrants had higher melanin levels than non-immigrants, but there was no difference in melanin by immigrants' length of stay in Canada.
- Melanin was weakly positively correlated with S-25(OH)D, with higher melanin levels associated with sociodemographic and environmental factors but not with indoor tanning use.

The robust associations between these factors and both skin melanin and S-25(OH)D levels highlight the potential of exploring the role of ethnicity and sociodemographic factors in designing national intervention programs to improve vitD status.

Introduction

Melanin is a natural pigment present in the skin that formulates skin color and that of other body parts such as hair and eyes [1, 2]. It is naturally produced in the human body and hair follicles, mainly by melanocytes. The degree of skin pigmentation depends on the degree of gene expression that controls the quality and quantity of melanin [1-4]. Melanin has many physiological benefits in maintaining health, with the most documented being that it acts as a sunscreen and protects the body from harmful ultraviolet (UV) radiation [3, 4]. Previous studies suggested that melanin may reduce body inflammation, prevent liver injuries and play a role in the immune system [5-7].

Vitamin D (vitD) is an essential fat-soluble nutrient with diverse biological functions that extend beyond the classical function of bone mineralization and skeletal maintenance. These extra functions include combating several chronic diseases, such as cardiovascular disease, hypertension, diabetes, cancer, and dermatological and autoimmune diseases [8-13].

Other non-classical functions of vitD include regulation of cellular differentiation, proliferation, apoptosis, and adaptive and innate immunity [14]. Following the discovery of the vitD receptor and several genetic polymorphisms that modulate the levels of vitD in the human body, increased attention has been directed toward genetic variations in different ethnic groups and how they variably interact in determining vitD levels [15].

Skin exposure to sunlight is the primary source of vitD3 synthesis (cutaneous synthesis) [16, 17], which primarily occurs in the upper skin layers. Because of its function as a biological shield against UV radiation, melanin inhibits cutaneous vitD3 synthesis. This is because dark skin pigmentation is mainly based on the eumelanin type (a dark brown/black bio-aggregate of melanin pigments derived from 5,6-dihydroxyindole-2-carboxylic acid and 5,6-

dihydroxyindole) located in the basal layer of the epidermis [17, 18]. Therefore, the higher melanin levels associated with dark skin require more sunlight exposure to produce sufficient vitD [19-21].

One in five Canadians is a first-generation immigrant and identified as foreign-born [22]. Canada's population is expected to increase by approximately 1 million foreign-born residents every 3 years by 2035/2036 [23]. Globally, immigrants to Western countries tend to have darker skin pigmentation than the native-born population of the host country. Moreover, darker-skinned immigrants in Canada and other Western countries have a high prevalence of vitD deficiency and insufficiency compared with Western people, with a deficiency prevalence of 19.3%–80% among different ethnic minorities [9, 19, 22, 24].

In our previous analysis of Canadian Health Measures Survey (CHMS) data, melanin levels were identified and used by Statistics Canada as an indicator of skin pigmentation (i.e., higher ranks indicated darker skin). That study concluded that immigrants' ethnic variation was the main predictor of/explanatory factor for lower S-25(OH)D among immigrants than among native-born Canadians. Other factors, including skin pigmentation (melanin level), were also associated with differences in S-25(OH)D levels [22]. However, no previous study has examined the relationship between melanin levels and S-25(OH)D among immigrants based on their ethnicity and region/country of birth compared with non-immigrants. Although the relationship between the two outcomes (vitD and melanin) is well established in the literature, this relationship has not been fully elucidated in the context of first-generation immigrants and inherent factors related to these immigrants. Therefore, the present study was designed to fill this knowledge gap and examine the relationship between melanin and vitD levels among first-generation immigrants from different ethnicities (more than 13 ethnicities) and origins or

countries of birth (more than 153 countries) compared with native-born Canadians. Moreover, we evaluated whether melanin levels could explain the variations in S-25(OH)D between immigrants and native-born Canadians. We hypothesized that melanin levels varied among CHMS participants based on their ethnicity and country of origin, which may explain the variations in S-25(OH)D.

Materials and methods

Study design and participants

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) planning, implementation, and reporting guidelines [25]. The study was part of a larger study investigating the association between vitD and health deterioration among first-generation immigrants in Canada [12, 22]. We used Cycle 3 (2012–2013) and Cycle 4 (2014–2015) of the CHMS data. The CHMS is a national cross-sectional population-based survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada [26]. The sample population weight was adjusted for age group and sex across Canada's five standard geographic regions: British Columbia, the Prairies, Ontario, Quebec, and the Atlantic Provinces [26, 27]. All participants provided written informed consent, and the CHMS survey was approved by the Health Canada Research Ethics Board [26].

Measures

Melanin level (index value) was measured in CHMS data as an indicator of the level of skin pigmentation. In this study, we used the data for melanin as the outcome-dependent factor. Melanin levels were measured from the back of the hand three times; a fourth measurement

was required if the difference between the first three melanin values deviated by more than 10 units. The final average calculated by Statistics Canada indicated the absolute index values of melanin. The higher the value, the more melanin is present in the epidermal and the darker the person's skin. The device used for measurement was the DSM II ColorMeter (Cortex Technology, Hadsund, Denmark) [28, 29]. Most previous immigration studies did not report the degree of skin pigmentation, and many studies used ethnicity or immigrants' country of origin as a proxy indicator for skin color [19]. However, we believe the measurement of skin melanin is a reliable indicator for skin pigmentation that enables investigation of correlations with S-25(OH)D among immigrants from different ethnicities and origins.

The S-25(OH)D level reflects total vitD intake from foods, supplements, and synthesis in the skin. We used mean S-25(OH)D as well as S-25(OH)D cut-off values to identify sufficient (≥50 nmol/L) or insufficient (<50 nmol/L) vitD status as defined by the Institute of Medicine and other expert reports [20, 30-32]. S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, MN, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L [22]. We also examined the CHMS data for use of indoor tanning equipment (e.g., beds, booths, and lamps) in the previous 12 months (recorded as 'yes' *vs.* 'no') in addition to the frequency (per day/week/month/year) and recent use during the last 2 months.

We assessed other independent variables that are known to be associated with or related to vitD status, melanin level or skin pigmentation, and immigration status. These factors were sex, age, ethnicity, body mass index (BMI, kg/m^2), smoking status, alcohol consumption, age at immigration, length of time in Canada, sun exposure, sunscreen use, season clothing (typically covered or uncovered), physical activity, region and country of birth, ethnicity,

intake of vitD-rich foods, use of indoor tanning equipment and vitD supplements. Details of these factors have previously been described [22].

Study population and CHMS details

We extracted data for 11,579 participants (21.9% immigrants) aged 3–79 years, with a mean (standard error [SE]) age of 39.23 (0.08) years. The study participants were previously defined as healthy (78.3%) and unhealthy (21.7%) in terms of the prevalence of chronic diseases that were diagnosed by healthcare professionals (12). Immigrants had lower concentration levels of S-25(OH)D (mean: 51·23 *vs*. 62·72; 95% confidence interval [CI]: 8·37, 14·62; $p<0·001$) compared with non-immigrants [22]. Information about the measurement methods, merging of the two data cycles and other CHMS data details are available on the Statistics Canada website (http://www.statcan.gc.ca, accessed on 24 February 2021) [33, 34], and our previous CHMS-related publications [12, 22].

Statistical analyses

To account for the unequal probability of selection and accurate estimates representing the Canadian population in our analyses, we used the survey command, recommended sample weight, and degrees of freedom. The unweighted results cannot be published (except for correlations) because of Statistics Canada's restrictions policy; therefore, the results are presented as weighted results only.

We used the mean (SE) for comparisons of continuous variables and proportions with 95% CI for categorical variables. Univariate analysis and multivariable linear regression modeling were used to identify factors associated with melanin levels. The models were adjusted for age, sex, immigration status, season, sun exposure, sunscreen use, clothing type, indoor

tanning use, smoking, alcohol, physical activity, and travel to sunny climates. Statistical significance was set at $P<0.05$. We used SPSS version 26.0 (IBM Corp., Armonk, NY, USA) to manage the data and Stata version 16.0 (StataCorp, College Station, TX, USA) to perform the analyses.

Results

The weighted total mean score for skin melanin levels was 16.46 (*SE*: 0.27; 95%*CI*: 15.90, 17.01). The mean value was higher among immigrants than non-immigrants (17.08 *vs.* 16.29, $p=0.004$), but no difference was found between recent (≤10 years) and well-established immigrants (>10 years). Melanin levels were weakly correlated with S-25(OH)D (≥50 nmol/L) ($r=0.088$; $P<0.001$). Sex (male), age (≥18 years), BMI (overweight), sun exposure (traveled to sunny climate), sunscreen (non-users), and smoking (currently smoking) were associated with higher melanin levels. The estimated use of indoor tanning beds and lamps among the Canadian population was 5.8% and was higher among non-immigrants than immigrants. The majority (63%) of indoor tanning users reported using tanning beds or lamps every year, and 2% reported at least one session in the last 2 months (data not shown). Melanin was not associated (users: 16.58 *vs*. non-users: 16.51; 95%*CI*: −0.61, 0.47) or correlated ($r=-0.019$; $p=0.079$) with the use of tanning equipment or the frequency of use. Moreover, no associations between melanin and clothing type, alcohol consumption, and the level of physical activity were observed (Table 1).

Table 1. Weighted mean melanin levels by S-25(OH)D, immigration, sociodemographic, and lifestyle factors using Canadian Health Measures Survey data (Cycles 3 and 4)

		Mean (SE)	**Mean difference (SE)**	**(95%CI)**	**P-value**	**r**	**P-value**
S-25(OH)D (nmol/L)	-	-				0.113	<0.001
S-25(OH)D (nmol/L)	<50 †	16.06 (0.28)					
	≥50	16.73 (0.26)	0.68 (0.18)	(0.30, 1.06)	0.001	0.088	<0.001
Immigration status	Non-immigrants †	16.29 (0.29)					
	Immigrants	17.08 (0.25)	−0.78 (0.24)	(−1.29, −0.281)	0.004	0.136	<0.001
Time after immigration (years)	≤10 †	17.05 (0.27)					
	>10	17.05 (0.31)	−0.01 (0.32)	(−0.67, 0.65)	0.978	−0.059	0.008
Sex	Male †	17.16 (0.29)	-	-			
	Female	15.75 (0.25)	1.41 (0.12)	(1.16, 1.65)	<0.00	−0.198	<0.001
Age (years)	<18 †	16.15 (0.35)					
	≥18	16.52 (0.25)	0.37 (0.14)	(0.07, 0.66)	0.017	0.092	<0.001
BMI (kg/m^2)	Normal weight †	16.40 (0.26)					
	Underweight	16.59 (0.38)	−0.18 (0.29)	(−0.78, 0.42)	0.542	−0.041	0.104
	Overweight	16.75 (0.27)	−0.34 (0.15)	-0.65, −0.035)	0.031	0.068	<0.001
	Obese	16.17 (0.32)	0.23 (0.18)	(−0.13, 0.60)	0.196	−0.017	0.0751
Sun exposure (min./day)	<30 †	16.01 (0.25)					
	≥30	16.51 (0.27)	−0.50 (0.18)	(−0.87, −0.13)	0.010	0.015	0.099
Sunscreen use	No †	17.13 (0.28)					
	Yes	16.21 (0.26)	0.93 (0.12)	(0.67, 1.18)	<0.00	−0.184	<0.001
Traveled to a sunny climate	No †	16.30 (0.28)					
	Yes	17.57 (0.25)	−1.30 (0.16)	(−1.59, −0.92)	<0.00	0.101	<0.001
Tanning equipment	No †	16.51 (0.25)					
	Yes	16.58 (0.37)	−0.07 (0.26)	(−0.61, 0.47)	0.788	−0.019	0.079
Clothing	Uncovered †	16.52 (0.29)					
	Covered	16.41 (0.26)	0.13 (0.14)	(−0.18, 0.34)	0.441	0.017	0.080
Smoking status	Former/never †	16.40 (0.25)					
	Current	16.91 (0.29)	−0.59 (0.16)	(−0.84, −0.17)	0.005	0.063	<0.001
Alcohol consumption	Former/never †	16.65 (0.30)					
	Current	16.47 (0.26)	0.18 (0.20)	(−0.24, 0.60)	0.388	−0.004	0.681
Meet physical activity	No †	16.40 (0.28)					
	Yes	16.55 (0.25)	−0.14 (0.16)	(−0.48, 0.19)	0.384	0.038	0.001

Correlation (*r*) weak or very weak (below +/− 0.3). SE, standard error; CI, confidence interval. Significant at $P<0.05$.

† Reference value.

Note: The mean S-25(OH)D (nmol/L) for each ethnicity was published in a previous paper [22].

People with white ethnicity had less pigmented skin than the non-white population (16.08 *vs*. 17.56) (r=0.243; P<0.001). Differences in melanin levels between different ethnic groups in the non-white population are presented in Table 2.

Table 2. Weighted mean melanin levels by ethnicity using Canadian Health Measures Survey data (Cycles 3 and 4)

	Mean (SE)	Mean difference (SE)	(95%CI)	P-value	r	P-value
White †	16.08 (0.29)					
Non-white	17.56 (0.25)	−1.54 (0.26)	(−2.07, −1.00)	<0.001	0.243	<0.001
Aboriginal	17.35 (0.44)	−0.93 (0.36)	(−1.67, −0.19)	0.016	0.045	<0.001
South Asian	17.70 (0.41)	−1.62 (0.49)	(−2.63, −0.61)	0.003	0.125	<0.001
Chinese	18.07 (0.60)	−1.99 (0.58)	(−3.18, −0.79)	0.002	0.151	<0.001
Black	19.66 (0.31)	−3.58 (0.40)	(−4.41, −2.74)	<0.001	0.262	<0.001
Filipino	17.06 (0.24)	−0.98 (0.35)	(−1.71, −0.25)	0.010	0.077	<0.001
Latin American	18.25 (0.43)	−2.18 (0.50)	(−3.21, −1.14)	<0.001	0.092	<0.001
Arab	15.88 (0.81)	0.20 (0.81)	(−1.47, 1.87)	0.804	0.033	0.002
Southeast Asian	16.74 (0.76)	−0.65 (0.76)	(−2.23, 0.92)	0.397	0.004	0.716
West Asian	16.26 (0.58)	−0.17 (0.63)	(−1.49, 1.13)	0.781	0.039	0.004
Korean	15.03 (1.70)	1.05 (1.70)	(−2.49, 4.58)	0.545	0.021	0.376
Japanese	16.41 (0.90)	−0.33 (0.93)	(−2.26, 1.60)	0.724	0.011	0.294
Multiple Ethnicities	16.84 (0.39)	−1.70 (0.89)	(−1.50, −0.13)	0.046	0.105	<0.001
Other Ethnicities	17.78 (0.99)	−0.76 (0.36)	(−3.56, 0.15)	0.070	0.064	<0.001

Correlation (r) weak or very weak (below +/− 0.3). SE, standard error; CI, confidence interval. Significant at P<0.05.

† Reference value.

Note: The mean S-25(OH)D (nmol/L) for each ethnicity was published in a previous paper [22].

Those who were born in South and Central America and the Caribbean, Africa, and Asia had higher melanin levels than people from Canada and North America. Differences in melanin were also observed by country of birth; the highest mean level was found among people born in Jamaica and the lowest among those born in Lebanon (Table 3).

Table 3. Weighted mean melanin levels by geographical region and country of birth using Canadian Health Measures Survey data (Cycles 3 and 4)

		Mean (SE)	Mean difference (SE)	(95%CI)	P-value	r	P-value
Region of birth	Canada and North America †	16.28 (0.30)	-	-	-		
	South and Central America and the Caribbean	18.80 (0.31)	−2.52 (0.35)	(−3.26, −1.79)	<0.001	0.121	<0.001
	Europe	16.29 (0.33)	−0.01 (0.29)	(−0.62, 0.59)	0.971	0.023	0.024
	Africa	17.44 (0.76)	−1.16 (0.73)	(−2.68, 0.36)	0.127	0.088	<0.001
	Asia	17.10 (0.26)	−0.81 (0.1)	(−1.45, −0.18)	<0.014	0.112	<0.001
Country of birth	Canada †	16.28 (0.30)	-	-	-		
	China	16.58 (0.43)	−0.30 (0.49)	(−1.3, 0.72)	0.546	0.021	0.040
	USA	16.03 (0.41)	0.24 (0.42)	(−0.62, 1.12)	0.560	0.005	0.619
	France	16.34 (0.92)	−0.06 0(.86)	(−1.86, 1.74)	0.946	−0.006	0.564
	Jamaica	20.32 (0.49)	−4.04 (0.45)	(−4.98, −3.10)	<0.001	0.077	<0.001
	UK	16.72 (0.67)	−0.44 (0.67)	(−1.84, 0.95)	0.517	0.008	0.408
	Algeria	15.31 (1.48)	0.97 (1.43)	(−2.00, 3.95)	0.504	−0.010	0.328
	Mexico	18.16 (1.28)	−1.88 (1.27)	(−4.53, 0.77)	0.156	0.023	0.027
	Pakistan	17.79 (0.79)	−1.51 (0.73)	(−3.04, 0.02)	0.052	0.048	<0.001
	Netherlands	16.60 (0.52)	−0.32 (0.51)	(−1.37, 0.73)	0.534	0.017	0.100
	India	18.62 (0.34)	−2.33 (0.40)	(−3.18, −1.50)	<0.001	0.113	<0.001
	Philippines	16.91 (0.22)	−0.63 (0.36)	(−1.38, 0.13)	0.101	0.050	<0.001
	Romania	16.86 (1.10)	−0.58 (1.10)	(−2.85, 1.70)	0.604	0.003	0.798
	Hong Kong	16.25 (0.55)	0.03 (0.66)	(−1.33, 1.40)	0.960	−0.003	0.743
	Germany	16.78 (1.12)	−0.51 (1.10)	(−2.77, 1.75)	0.443	0.024	0.046
	Colombia	16.90 (0.84)	−0.62 (0.96)	(−2.60, 1.37)	0.525	0.033	0.002
	Morocco	16.35 (1.68)	−0.07 (1.66)	(−3.51, 3.37)	0.968	0.011	0.270
	Italy	15.59 (0.80)	0.69 (0.75)	(−0.88, 2.25)	0.371	0.004	0.722
	Iran	16.37 (0.30)	−0.09 (−0.86)	(−1.86, 1.69)	0.920	0.020	0.049
	Lebanon	15.40 (0.28)	0.88 (0.36)	(0.13, 0.6)	0.023	−0.004	0.691
	Other	17.08 (0.26)	−0.80 (0.28)	(−1.39, −0.21)	0.010	0.125	<0.001
	All (153 countries)	16.99 (0.23)	0.71 (0.24)	(−1.22, −0.21)	0.008	0.138	<0.001

Correlation (*r*) weak or very weak (below +/− 0.3). SE, standard error; CI, confidence interval. Significant at $P<0.05$.

† Reference value.

Note: The mean S-25(OH)D (nmol/L) for each region\country of birth was published in a previous paper [22].

In the adjusted multivariate linear regression model, factors associated with skin melanin levels were S-25(OH)D, immigration status, sex, age, summer and fall seasons, travel to a sunny climate, sun exposure, sunscreen use, smoking, and alcohol consumption (Table 4).

Table 4. Multivariable linear regression analysis based on melanin and immigration status using Cycles 3 and 4 of Canadian Health Measures Survey data

	Melanin level		
	Beta estimate (SE)	**(95%CI)**	**P-value**
S-25(OH)D (*nmol/L*)	0.01 (0.004)	(0.001, 0.02)	0.039
Immigration status (immigrant)	0.62 (0.21)	(0.17, 1.06)	0.009
Sex (female)	−1.64 (0.14)	(−1.92, −1.35)	<0.001
Age	0.02 (0.004)	(0.01, 0.03)	<0.001
Season (summer)	2.69 (0.42)	(1.80, 3.57)	<0.001
Season (fall)	1.75 (0.43)	(0.84, 2.65)	0.001
Sun exposure (yes)	0.48 (0.19)	(0.09, 0.87)	0.017
Traveled to a sunny climate (yes)	1.44 (0.19)	1.04, 1.84)	<0.001
Sunscreen use (yes)	−0.45 (0.13)	(−0.73, −0.18)	0.002
Smoking (current)	0.67 (0.16)	(0.28, 0.94)	0.001
Alcohol (current)	−0.52 (0.16)	(−0.84, −0.19)	0.003
Const.	14.45 (0.73)	(12.93, 15.98)	<0.001

Linear regression adjusted for immigration status, S-25(OH)D, age, sex, season, sun exposure, sunscreen use, clothing, tanning, smoking, alcohol, physical activity, and travel to a sunny country.

SE, standard error; CI, confidence interval. Significant at P<0.05.

Discussion

This study explored the associations between melanin levels and participants' sociodemographic characteristics and clarified whether melanin levels explained the variations in vitD between immigrants compared with native-born Canadians. Our investigation of melanin levels among immigrants and the association between melanin and S-25(OH)D revealed that immigrants had higher melanin levels (darker skin) compared with non-immigrants, but there was no difference in melanin by their length of stay in Canada.

However, melanin had a weak positive correlation with S-25(OH)D levels; this finding contradicted existing knowledge and implied there may be different confounding factors that may interfere with the relationship between melanin levels and vitD in the present cross-sectional observational design. This can be explained also by the fact that although epidemiological studies suggest that melanin inhibits cutaneous vitamin D synthesis by UVB radiation; however, laboratory investigations assessing the impact of melanin on vitamin D production have produced contradictory results. Young et al found that melanin has a small inhibitory effect on vitamin D synthesis [21]. Moreover, in vitiligo where we have a destruction of functional melanocytes it has been found that the application of vitamin D might help in preventing the destruction of melanocytes. This may be through the effect of vitamin D on the intracellular Ca^{+2}, which controls the activity of thioredoxin reductase. The latter is important for thioredoxin, which stimulates tyrosinase activity, the principal enzyme involved in melanin synthesis [35]. Therefore, the relationship between melanin serum levels and vitamin D is a bit complicated. We know that exposure to sunlight will lead to darker skin due to increased levels of melanin to protect the skin from the effect of UVB radiation. Meanwhile, for the synthesis of vitamin D, we need to be exposed to sunlight. Hence, sun avoidance may result in decreased melanin levels and low vitamin D levels. This can explain, at least partially, the positive correlation between melanin and vitamin D levels. This is supported by a study by Glass et al who reported that Caucasian UK females with fair skin types show lower levels of 25(OH)D compared to darker skin types [36].

Previous immigration studies concluded that ethnicity and lifestyle changes, including dietary changes after immigration, along with slow physiological adaptation to the new environment (e.g. lower UV radiation level at the new latitude) mean that immigrants have low levels of S-

25(OH)D [13, 19, 24, 37]. Moreover, a higher level of skin pigmentation has also been suggested to contribute to lower S-25(OH)D levels [19, 22, 37-39]. In the same context, another study found melanin had a slight inhibitory effect on the photosynthesis of vitD3 among healthy participants who had skin types II-VI (white to black) [21].

Evidence indicates that the length of residency in Canada after immigration is associated with equitable environmental and lifestyle acculturation [22, 40, 41]. Moreover, the length of stay in the host country was also associated with the lightening of skin color as part of the genomic adaptation process [42]. However, we found no differences in skin melanin levels between recent and well-established immigrants. Similarly, we found a weak negative correlation between skin melanin and longer residency duration in Canada, which may be explained by the slight lightening of skin over time due to slow genomic adaptation [42].

In our previous related publication [22], the multivariate analysis showed that the S-25(OH)D level was found positively associated with age (Beta Estimate(SE) 0.14 (0.04)). The lowest S-25(OH)D levels were found among the youth aged 12–17 years. Few studies have sought to define the difference in melanin levels/skin pigmentation in terms of sociodemographic (e.g. sex, age, and BMI) and behavioral variations (e.g. smoking, physical activity, and indoor tanning), and no available studies have considered immigrants' country of birth or ethnicity [43-45].

Consistent with our finding of higher melanin levels among males and older people, a previous study reported a higher melanin index among men compared with women and among people aged 20–30 years compared with those aged 10–20 years [44]. Lighter skin among older people was reported to be caused by a decrease in the number of melanocytes, which is estimated to decrease by around 8%–20% per decade [46]. Our findings of higher melanin

levels among non-sunscreen users, those who were exposed to the sun (including traveling to sunny climates), and current smokers were consistent with previously published research [21, 43, 44, 47, 48].

The significantly higher melanin levels among overweight people compared with those with normal body weight noted in this study were consistent with the involvement of melanin in the expression of components of the melanogenic pathway in the adipocytes. A previous study found that relative to lean people, the adipose tissue of obese patients had higher amounts of melanin, which is known for its antioxidant and anti-inflammatory properties that help in scavenging reactive oxygen species and suppress oxidative stress and inflammation in adipocytes [45].

Indoor tanning use is increasing and becoming a widespread industry that is now more accessible to the public. Tanning machines emit UV light, which can theoretically increase S-25(OH)D levels. However, the Endocrine Society reported that tanning caused darkening of the skin by increasing melanin production, which aims to protect the skin against the damaging effect of UV radiation; this high melanin production limits the ability of the skin to synthesize more vitD [49]. However, we found that only 2% of the CHMS participants reported indoor tanning in the last 2 months, and the use of tanning equipment did not significantly impact skin melanin levels, although this may be affected by the frequency and duration of tanning equipment use. Moreover, knowledge about melanin synthesis, migration to the skin, degradation, and the impact on S-25(OH)D concentration is not well established [50]. Therefore, other confounding factors may impact the effect of tanning UV exposure among immigrants (darker skin) and non-immigrants (lighter skin).

The notable variation in melanin levels among immigrants from different ethnicities and origins in this study could be explained by genetic and epigenetic (potential genetic changes that affect gene expression without involving changes in the original sequence of DNA nucleotides) variations in melanogenesis [51]. Melanogenesis is a complex process in which melanin is synthesized in melanocytes and transported to keratinocytes. This process involves multiple signaling pathways and genes [48].

An important factor that helps to understand variations in S-25(OH)D levels in response to skin melanin levels is skin type. Different skin types (e.g. Fitzpatrick skin type [FST] I–VI) have been shown to behave differently in response to exposure to UV radiation; therefore, the inhibitory effect of skin melanin on vitD synthesis varies [52]. Recent work by Young et al. revealed that skin type II was significantly steeper than the other groups in relation to vitD levels after exposure to UV radiation, and a comparison between extreme skin types (II and VI) showed melanin inhibition factors of approximately 1.3–1.4 [21].

The present study is a continuation of our previous work [12, 13, 22], which revealed that ethnicity and sociodemographic factors were the factors most strongly associated with S-25(OH)D. Japanese, Arabs, and Southeast Asians were found to have the lowest S-25(OH)D levels and the most deficient ethnic groups compared with the white group [22]. Demonstrating robust associations between these factors and both skin melanin and serum vitD levels reinforces the value of considering the role of ethnicity and various sociodemographic factors when designing national intervention programs to improve vitD status.

In addition to offering national and representative data, the strengths of the CHMS include the study design and large sample size that captured the ethnocultural diversity of immigrants

from more than 150 countries and over 13 major ethnic groups. Moreover, melanin level based on the DSM II ColorMeter method is a reliable indication of skin pigmentation. The DSM II ColorMeter method had similar diagnostic characteristics to FST for discerning vitD deficiency and therefore offers an inexpensive, useful surrogate measure of skin color in vitD research [28, 29]. However, both methods have been criticized for their limitations in skin classification and imprecisely measuring skin color and reflecting melanin levels [29]. Based on a recent systematic review and meta-analysis of reliable tools for assessing skin color [29], we recommend further research uses more reliable tools. In addition, further studies are warranted to elucidate the precise genetics underpinning skin color adaptation and the genetic architecture of skin color adaptation in different ethnic groups. Developing this knowledge will help to address gaps in the literature. An important limitation of our study was that we could not infer causality because of the cross-sectional observational design.

Conclusion

Skin melanin levels appeared to be associated with several sociodemographic and behavioral characteristics. First-generation immigrants had higher melanin levels (darker skin) than non-immigrants, but there was no difference in melanin related to their length of stay in Canada. The weak positive correlation between melanin and S-25(OH)D levels in this study suggested the involvement of various environmental (e.g. dietary and behavioral) confounders and genetic factors that may interfere with the relationships between melanin level, vitD, and immigration status.

Declarations

Author contributions: SY and GW conceived the study. With close supervision from GW, SY managed the data, verified the analytical methods, and prepared the tables and figures. AH

verified the underlying data at the Research Data Center. SY, MF, and HH interpreted the results. SY prepared the final draft. All authors including IC, MP, DM, AH, MF, and HH contributed to the design and analysis of the research, and substantive review of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CHMS data were obtained and supported by funding to the Canadian Research Data Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. Although the research and analyses were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Ethics approval: Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Institutional review board statement: All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025). The Health Canada Research Ethics Board approved the CHMS.

Informed consent statement: Statistics Canada collected written consent from all participants for a personal interview, physical measures, and biospecimens collection.

Data availability statement: Data described in the manuscript, codebook, and analytic code will not be publicly available because these data are confidential national data hosted by Statistics Canada.

Acknowledgments: The authors acknowledge the Carleton, Ottawa, Outaouais Local Research Data Centre team for assistance with access to CHMS data.

Conflicts of interest: The authors declare no personal or financial conflicts of interest.

References

1. Boissy, R.E., *Melanosome transfer to and translocation in the keratinocyte.* Experimental dermatology, 2003. **12**: p. 5-12.
2. Mapunya, M.B. and N. Lall, *Melanin and Its Role in Hyper-Pigmentation–Current Knowledge and Future Trends in Research*, in *Breakthroughs in Melanoma Research*. 2011, IntechOpen.
3. Markiewicz, E. and O.C. Idowu, *Melanogenic Difference Consideration in Ethnic Skin Type: A Balance Approach Between Skin Brightening Applications and Beneficial Sun Exposure.* Clinical, cosmetic and investigational dermatology, 2020. **13**: p. 215.
4. Schlessinger, D.I., M. Anoruo, and J. Schlessinger, *Biochemistry, melanin*, in *StatPearls [Internet]*. 2021, StatPearls Publishing.
5. Xu, C., et al., *The structural analysis and its hepatoprotective activity of melanin isolated from Lachnum sp.* Process Biochemistry, 2020. **90**: p. 249-256.
6. Hung, Y., et al., *Protection of tea melanin on hydrazine-induced liver injury.* Life Sciences, 2003. **72**(9): p. 1061-1071.
7. Mohagheghpour, N., et al., *Synthetic melanin suppresses production of proinflammatory cytokines.* Cellular Immunology, 2000. **199**(1): p. 25-36.
8. Torequl Islam, M., et al., *HIGH SKIN MELANIN CONTENT, VITAMIN D DEFICIENCY AND IMMUNITY: POTENTIAL INTERFERENCE FOR SEVERITY OF COVID-19.* FARMACIA, 2020. **68**: p. 6-6.
9. Renzaho, A.M.N., J.A. Halliday Bhsci, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review.* Nutrition, 2011. **27**: p. 868-879.
10. Peterlik, M., et al., *Vitamin D and calcium insufficiency-related chronic diseases: an emerging world-wide public health problem.* International journal of environmental research and public health, 2009. **6**(10): p. 2585-2607.
11. Ghasemian, R., et al., *The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis.* medRxiv, 2021: p. 2020.06.05.20123554-2020.06.05.20123554.
12. Yousef, S., et al., *Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data.* Nutrients, 2022. **14**(9): p. 1760.
13. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis.* Systematic Reviews, 2019. **8**(1): p. 1-6.
14. Umar, M., K.S. Sastry, and A.I. Chouchane, *Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies.* International journal of molecular sciences, 2018. **19**(6): p. 1618.

15. Amanzholkyzy, A., et al., *Ethnic Manifestations of Gene Polymorphisms of Vitamin D Receptor (VDR) in Adolescents of Western Kazakhstan Region.* J Natl Med Assoc, 2018. **110**(1): p. 78-83.

16. Jablonski, N.G. and G. Chaplin, *Human skin pigmentation, migration and disease susceptibility.* Philosophical Transactions of the Royal Society B: Biological Sciences, 2012. **367**(1590): p. 785-792.

17. Carlberg, C., *Vitamin D and Pigmented Skin*. 2022, Multidisciplinary Digital Publishing Institute. p. 325.

18. Ito, S. and K. Wakamatsu, *Quantitative analysis of eumelanin and pheomelanin in humans, mice, and other animals: a comparative review.* Pigment cell research, 2003. **16**(5): p. 523-531.

19. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.

20. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

21. Young, A.R., et al., *Melanin has a small inhibitory effect on cutaneous vitamin D synthesis: A comparison of extreme phenotypes.* Journal of Investigative Dermatology, 2020. **140**(7): p. 1418-1426. e1.

22. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.

23. StatisticsCanada. *Population Projections for Canada, provinces and Territories*. 2014 [cited 2021 20/11/2021]; Available from: https://www150.statcan.gc.ca/n1/en/pub/91-520-x/91-520-x2010001-eng.pdf?st=LWFifucU.

24. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D*, in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.

25. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*.* Bulletin of the World Health Organization, 2007. **85**(11): p. 867-872.

26. Day, B., et al., *Canadian Health Measures Survey: Ethical, legal and social issues*. 2007.

27. Ng, E., *Canadian Health Measures Survey: A tool for immigrant health research?* Statistics Canada, Health Report, 2015.

28. Khalid, A.T., et al., *Utility of sun-reactive skin typing and melanin index for discerning vitamin D deficiency.* Pediatric research, 2017. **82**(3): p. 444-451.

29. Langeveld, M., et al., *Skin measurement devices to assess skin quality: A systematic review on reliability and validity.* Skin Research and Technology, 2022. **28**(2): p. 212-224.

30. Ross A. Catharine, et al., *DIETARY REFERENCE INTAKES Calcium Vitamin D Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board*. 2011.

31. Vieth, R., *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml).* Best Practice & Research Clinical Endocrinology & Metabolism, 2011. **25**: p. 681-691.

32. Dawson-Hughes, B., *Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment - UpToDate*. 2021.

33. StatisticsCanada, *Canadian Health Measures Survey, Cycle 4, 2014-2015 - Privacy impact assessment summary*. 2014-2015.

34. StatisticsCanada. *Canadian Health Measures Survey, Cycle 3, Privacy impact assessment* 2012-2013; Available from: https://www.statcan.gc.ca/eng/about/pia/chmsc3.

35. Oikawa, A. and M. Nakayasu, *Stimulation of melanogenesis in cultured melanoma cells by calciferols.* FEBS letters, 1974. **42**(1): p. 32-35.

36. Glass, D., et al., *Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK.* PLoS One, 2009. **4**(8): p. e6477.

37. Cashman, K.D., et al., *Vitamin D deficiency in Europe: pandemic?* The American journal of clinical nutrition, 2016. **103**(4): p. 1033-44.

38. Nimitphong, H. and M.F. Holick, *Prevalence of Vitamin D Deficiency in Asia Vitamin D status and sun exposure in Southeast Asia.* Dermato-endocrinology, 2013. **5**(1): p. 34-37.

39. Bonilla, C., et al., *Skin pigmentation, sun exposure and vitamin D levels in children of the Avon Longitudinal Study of Parents and Children.* BMC Public Health, 2014. **14**(1): p. 1-10.

40. Sanou, D., et al., *Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.

41. Salant, T. and S.L. Diane, *Measuring culture: a critical review of acculturation and health in Asian immigrant populations.* Social Science & Medicine, 2003. **71**: p. 71-90.

42. Carlberg, C., *Nutrigenomics of vitamin D.* Nutrients, 2019. **11**(3).

43. Haresaku, S., et al., *Association of lip pigmentation with smoking and gingival melanin pigmentation.* Oral diseases, 2007. **13**(1): p. 71-76.

44. Firooz, A., et al., *Variation of biophysical parameters of the skin with age, gender, and body region.* The Scientific World Journal, 2012. **2012**.

45. Page, S., V. Chandhoke, and A. Baranova, *Melanin and melanogenesis in adipose tissue: possible mechanisms for abating oxidative stress and inflammation?* obesity reviews, 2011. **12**(5): p. e21-e31.

46. Costin, G.-E. and V.J. Hearing, *Human skin pigmentation: melanocytes modulate skin color in response to stress.* The FASEB journal, 2007. **21**(4): p. 976-994.

47. Cho, Y.H., et al., *Changes in skin color after smoking cessation.* Korean Journal of Family Medicine, 2012. **33**(2): p. 105.

48. Solano, F., *Photoprotection versus photodamage: Updating an old but still unsolved controversy about melanin.* Polymer International, 2016. **65**(11): p. 1276-1287.

49. TheEndocrineSociety. *Tanning may protect skin against harmful UV irradiation but block vitamin D synthesis*. 2016 [cited 2022 May 24th, 2022]; Available from: www.sciencedaily.com/releases/2016/04/160403152337.htm.

50. Pham, T., *Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal.* Thesis-McGill University, 2012.

51. Zhou, S., et al., *Epigenetic regulation of melanogenesis.* Ageing research reviews, 2021. **69**: p. 101349.

52. Fitzpatrick, T.B., *The Validity and Practicality of Sun-Reactive Skin Types I Through VI.* Archives of Dermatology, 1988. **124**(6): p. 869-871.

3.3 Vitamin D and Chronic Diseases among First-Generation Immigrants

Section overview

We used the presence of CDs (e.g., diabetes, heart disease, cancer, inflammatory lung diseases, and asthma) and CD-related biomarkers as proxy indicators to investigate risk factors for health deterioration in the context of vitamin D status. Other attributes such as date of immigration and mobile clinic visit dates (e.g., blood sampling including S-25(OH)D), were also used.

Immigrants had a lower prevalence of CDs than native-born Canadians. Immigrants who came to Canada aged ≥ 18 years had more CDs than those younger than 18 years. There was no difference in the prevalence of CDs before immigration compared with post immigration. However, using two different time points (5 and 10 years), we found that the longer immigrants had lived in Canada, the higher the prevalence of CDs, which may be considered an early sign of health deterioration. Our study concluded that accumulated lower levels S-25(OH)D may impact the health profile of immigrants in terms of changing CD-related biomarkers. Thus, deviations in CD-related biomarkers and environmental and lifestyle changes after immigration may play crucial roles in subsequent health deterioration among immigrants.

Manuscript status

This manuscript has been published: *Nutrients 2022, 14(9), 1760;*

https://doi.org/10.3390/nu14091760

Said Yousef*, Ian Colman, Manny Papadimitropoulos, Douglas Manuel, Alomgir Hossain, MoezAlIslam Faris, and George A. Wells.

Author contributions

SY and GW conceived this study. With close supervision from GW, SY managed the data, verified the analytical methods, and prepared the tables and figures. AH verified the underlying data at the Research Data Center. SY interpreted the results and prepared the final draft. All authors including IC, MP, DM, and MF, contributed to the design and analysis of the research, and the substantive review of the manuscript.

Related thesis appendices

Appendix A3:

The PDF of the published manuscript is presented in Appendix A3.3.

Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data

Said Yousef *, Ian Colman, Manny Papadimitropoulos, Douglas Manuel, Alomgir Hossain, MoezAlIslam Faris, and George A. Wells

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Douglas Manuel, MD, MSc.
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

MoezAlIslam Faris, Ph.D.

Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Background: Nearly 22% of the Canadian population are first-generation immigrants. We investigated immigrants' health status and health deterioration over time in terms of the prevalence of chronic diseases (CDs) and their relationship to vitD status.

Methods: We used cycles three (2012–2013) and four (2014–2015) of the Canadian Health Measures Survey. These data contained unique health information and direct physical/blood measures, including serum 25-hydroxyvitamin D (S-25(OH)D). Indicators of health status and deterioration were the prevalence of CDs diagnosed by healthcare professionals, self-reported general and mental health, and CD-related biomarkers.

Results: The data (n= 11,579) included immigrants from more than 153 countries. Immigrants were healthier than non-immigrants for most health status measures. The prevalence of CDs was higher among those who migrated to Canada aged ≥18 years. A longer time in Canada after immigration was associated with a higher risk for CDs. The mean S-25(OH)D was lower among immigrants, higher among patients with CDs, and inversely associated with glycated hemoglobin, total cholesterol/high-density lipoprotein ratio, immunoglobulin E, serum ferritin, and blood hemoglobin. After adjusting for covariates, no association was found between S-25(OH)D and the prevalence of CDs.

Conclusion: Lower levels of accumulated S-25(OH)D among immigrants may impact their health profile in terms of CD-related biomarkers, which partially explains immigrants' health deterioration over time. We recommend further longitudinal research to investigate immigrants' vitD and health deterioration.

Keywords: immigrants' health deterioration; vitamin D; serum 25-hydroxyvitamin D; chronic diseases.

Summary of the key issues and findings

- Extensive research evidence indicates that Canadian immigrants tend to be healthier at the time of immigration than well-established immigrants and non-immigrants. This "healthy immigrant" effect lessens over time for immigrants living in Canada. Nevertheless, immigrants are at higher risk for vitD deficiency compared with non-immigrants, with the risk highest in younger and more recent immigrants. The longer an immigrant lived in Canada, the better their serum vitD levels; ethnicity was also a significant indicator of vitD deficiency.

- This study highlighted that immigrants tend to have better health than their counterparts in terms of the prevalence of chronic diseases (CDs) such as heart disease, cancer, asthma, and inflammatory lung diseases, but there is no difference in self-rated general and mental health. In contrast, CD-related biomarkers (e.g., glycated hemoglobin and total cholesterol/high-density lipoprotein cholesterol ratio) and serum vitD differed in favor of non-immigrants. There was no difference in the pre-migration prevalence of CDs compared with post-immigration; however, the longer immigrants lived in Canada, the higher the prevalence of CDs. The adjusted regression model showed serum vitD was not associated with CDs. Our findings suggest the cumulative impact of lower serum vitD among immigrants over time, changing biomarkers, and environmental and lifestyle changes after immigration may play crucial roles in subsequent health deterioration among immigrants.

- Further longitudinal research is needed to clarify immigrants' health deterioration and the complicated and controversial bidirectional association between serum vitD and CDs. For instance, immigrants may be followed over their residency in their host country to explore the patterns, developments, and direction of health deterioration.

1. Introduction:

Immigrants are a fundamental part of the Canadian population and policy framework [1], with nearly 22% of the Canadian population being first-generation immigrants [2]. Statistics Canada estimated an increase of approximately 1 million foreign-born residents every 3 years by 2035/2036 [3]. Therefore, the health of immigrants will impact Canada's overall future healthcare system.

Accumulated evidence suggests that recent immigrants have better health than people of the host country, including long-term immigrants who had previously migrated to the host country. This phenomenon is called the "healthy immigrant effect" or "healthy immigrant advantage" [4-6]. However, immigrants' physical and mental health declines after arrival in Canada, with health changes often occurring within 5–10 years [4, 5]. Pre-migration factors, such as rigorous selection criteria that favor immigrants that are healthier, wealthier, and better educated, along with post-immigration factors, such as environmental and lifestyle changes, may explain this health decline after migration [4, 7-10]. In addition, the healthy immigrant effect varies through the course of life [6].

Moreover, more immigrants have deficient and insufficient vitamin D (vitD) levels compared with native-born populations [2,11,12]. However, vitD status varies among immigrants because of ethnic variations, skin pigmentation, resettlement changes in diet, physical activity, and sun exposure [2,11,13,14]. The concentration of serum 25-hydroxyvitamin D (S-25(OH)D) represents the combined contributions of the cutaneous synthesis and dietary intake of vitD and is considered the most important clinical marker for the overall vitD level [12,15,16]. A lower concentration of S-25(OH)D was found to be a risk factor for CDs [11-14]

and could predict all-cause mortality [17,18,21]. Moreover, Jablonski et al. expected the diseases associated with vitD deficiency to be a major source of morbidity and mortality in the 21st century [15]. Most recent guidelines have emphasized the importance of vitD for skeletal health, although evidence supporting its benefits for non-skeletal health outcomes is either weak or conflicting [16, 17]. There is a range of recommended vitD thresholds that are used to study health effects. Mean S-25(OH)D (nmol/L) values or ranges at various thresholds (e.g., deficiency: 25–30 nmol/L; insufficiency: 25–49 nmol/L; and sufficiency: 50–75 nmol/L) are commonly used in studies to describe vitD status [18]. An insufficient vitD level (<50 nmol/L) is more frequently used to describe hypovitaminosis D [19].

VitD deficiency has been linked to physical and mental illnesses [20, 21]. Recent research supported the hypothesis that vitD deficiency was related to the incidence, severity [22, 23], and mortality attributed to COVID-19 [23, 24]. These studies concluded that those at the highest risk for severe COVID-19 matched those at the highest risk for severe vitD deficiency, including older people, darker-skinned ethnic groups, and obese people [28,30,31]. Moreover, research has highlighted the importance of further studies investigating immigrants' health deterioration in the context of vitD [2, 25], lifelong adversity [26], and changes in lifestyle and dietary intake [5, 25]. However, leading causes of death, such as CDs (cardiovascular disease, cancer, chronic lung disease, and diabetes), are used as reliable measures for public health [27]. The main objective of this study was to investigate immigrants' health status and possible health deterioration in relation to serum vitD levels. Moreover, we used CDs and CD-related biomarkers as proxy indicators to investigate risk factors for health deterioration in the context of vitD status. In addition, we compared the health status (in relation to the vitD status) of immigrants from different ethnic groups and origins with non-immigrants.

2. Materials and Methods

2.1. Study Design and Participants

We previously published the main characteristics, mean S-25(OH)D levels, and prevalence and leading determinants of vitD deficiency/insufficiency among immigrants and non-immigrants in Canada [2]. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement in the planning, implementation, and reporting [28].

Health and vitD status among first-generation immigrants (foreign-born) were ascertained using Canadian Health Measures Survey (CHMS) data and compared with those in the non-immigrant (native-born) population. The CHMS represents the first national data on vitD, includes the Canadian immigrant population, addresses gaps in existing national information, and contains unique health information, including direct physical and blood measures [29, 30]. The sample size for each CHMS cycle was carefully selected to provide a reliable and representative estimate at the national level for sex and age groups. The survey covered approximately 96% of the Canadian population. A dwelling stratification stage was applied, followed by a roster list of all people living in each household, from which individuals aged 3–79 years were randomly selected [29, 30]. The CHMS sample population weight was adjusted for age and sex across Canada's five standard geographic regions. All participants provided written informed consent, and the CHMS was approved by the Health Canada Research Ethics Board [29, 30].

2.2. Measures

The S-25(OH)D is expressed in nanomoles per liter (nmol/L) and is measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, MN, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. We used S-25(OH)D cut-off points to identify vitD status as either sufficient (≥50 nmol/L) or insufficient (<50 nmol/L), as defined by the Institute of Medicine (IOM) and other experts [12,38,39].

We used the presence of CDs as the outcome-dependent factor for health deterioration. CDs included 24 chronic diseases and conditions (e.g., type 1 and 2 diabetes, heart disease (not limited to ischemic heart disease), and mood disorder). Respondents were asked "Do you have a long-term condition that was diagnosed by a healthcare professional and expected to last or has already lasted 6 months or more?" (yes/no). We used CDs (e.g., diabetes, heart disease, cancer, and asthma) for which a date of diagnosis was listed. We combined CDs that had similar inflammatory characteristics (including, but not limited to chronic obstructive pulmonary disease, bronchitis, and emphysema) as one variable called "inflammatory lung diseases." Inflammatory lung diseases were measured for participants aged >29 years, but no date of diagnosis was available. CDs were considered present if at least one of the five listed health conditions (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases) received a "yes" response as a separate variable called "CDs." The date of diagnosis for the CDs was not available.

Our analysis examined: five health conditions (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases), CDs (at least one), self-rated general health, and self-rated mental health. We also considered seven biomarkers associated with CDs: glycated hemoglobin (HbA1c), the total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL ratio), high-

sensitivity C-reactive protein (hs-CRP), immunoglobulin E (IgE), ferritin, hemoglobin (Hb), and S-25(OH)D (the serum concentration of vitD). In addition, 16 sociodemographic and health behavior variables were examined as independent factors: immigration status, sex, age, income, education level, body mass index (BMI; kg/m2), smoking status, alcohol consumption, age at immigration, length of time in Canada, physical activity, region, country of birth, ethnicity, dairy intake, and vitD supplement use.

The CHMS was a cross-sectional survey. Data for health measures, including several temporal attributes such as date of immigration and mobile clinic visit dates (e.g., blood sampling including S-25(OH)D), were used to create proxy health indicators for health deterioration. To examine longitudinal changes in health, we created a new variable to compare "diagnosis before immigration" versus "diagnosis after immigration." We also created a new variable "time after diagnosis" to investigate the relationship between S-25(OH)D and the presence of CDs. We used two categories (recent vs. long-term) for diagnosis at two time-points (1 year and 5 years). We used the lowest cut-off value to represent the most recent S-25(OH)D measures at the date of diagnosis (e.g., ≤1 year and ≤5 years) and the highest to represent the long-term measures for S-25(OH)D at the date of diagnosis (e.g., >1 year and >5 years).

A Likert scale was used for the two self-reported questions that reflected the quality of general and mental health. Participants aged over 12 years rated these questions, with the ratings for each question dichotomized in two categories: "fair/poor" versus "good" (excellent/very good/good).

Detailed information about the CHMS data, methods, and merging of the two cycles can be found in our previous work [2] and on the Statistics Canada website (http://www.statcan.gc.ca,

accessed 14 February 2021) [31, 32]. The method of measurement and the analytical detection limit for each biomarker are available in Appendix A, Table A1.

2.3. Statistical Analysis

Following the recommendations of Statistics Canada, all analyses used population weights that reflected the probability a respondent was included in the survey. Descriptive statistics were used to investigate immigrants' demographic, clinical, and behavioral characteristics compared with non-immigrants. We used the mean and standard error (SE) for continuous variables. Data were stratified based on the study outcomes (CDs) and variables of interest (e.g., immigration status). To account for the unequal probability of selection and present an accurate estimate of the Canadian population, we used the survey command, recommended sample weight, and degrees of freedom in the analyses. Therefore, all results were weighted values. In addition to the two S-25(OH)D cutoff points (sufficient ≥50 nmol/L and insufficient <50 nmol/L), we used the continuous values for S-25(OH)D and other biomarkers.

We used univariate analyses to identify independent covariates. Multivariable logistic regression models (odds ratio (OR) and 95% confidence interval (CI)) were then used to evaluate the association between CDs (indication of health deterioration) and vitD status for immigrants compared with non-immigrants. The final model was adjusted for immigration status, age, sex, household income, education, ethnicity, BMI, physical activity, smoking behavior, alcohol consumption, vitD supplement use, HbA1c, the TC/HDL ratio, Hb, ferritin, IgE, and hs-CRP. Statistical significance was set at $p \leq 0.05$. All analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Stata version 16.0 (StataCorp, College Station, TX, USA).

3. Results

We examined data for 11,579 CHMS participants, including immigrants from more than 153 countries. The main characteristics of the study sample have previously been published *[2]*. The prevalence rates of CDs based on the sociodemographic and immigration characteristics of all study participants are presented in Table 1. Immigrants had a lower prevalence of CDs than non-immigrants. Those who had migrated to Canada at age ≥18 years had a higher prevalence of CDs than those who migrated at under 18 years of age. At two different time points after the migration (5 and 10 years), the prevalence was higher among those who had stayed in Canada for ≥5 years and ≥10 years than among those who had stayed less than 5/10 years. The prevalence of CDs was higher among immigrants with older age, lower household income, underweight, overweight, and obesity compared with their younger, higher income, and average body weight counterparts. Participants who did not meet the Canadian physical activity recommendations had a higher prevalence of CDs.

Table 1. Weighted prevalence of chronic diseases by sociodemographic and behavioral characteristics and immigration status.

		No CDs † (78.3%), %	CDs (21.7%), %	P-value
Immigration status	Non-immigrant †	76.80	23.20	<0.001
	Immigrant	83.36	16.64	
Age at immigration, years	<18 years †	91.69	8.31	<0.001
	≥18	74.75	25.25	
Years after immigration	≤5 years †	91.72	8.28	0.004
	>5	80.98	19.02	
Years after immigration	≤10 years †	92.84	7.16	<0.001
	>10	77.34	22.66	
Sex	Male †	78.67	21.33	0.641
	Female	77.88	22.12	
Age group, years	<5	92.92	7.08	<0.001
	5–11	89.83	10.17	
	12–17	85.14	14.86	
	18–64 †	80.01	19.99	
	>64	52.7	47.3	
Household income (CAD)	<50,000	72.34	27.66	<0.001
	50,000–100,000 †	80.35	19.65	
	>100,000	83.09	16.91	
BMI (kg/m^2)	Underweight	75.95	24.05	<0.001
	Normal weight †	84.72	15.28	
	Overweight	78.64	21.36	
	Obese	67.56	32.44	
Physical activity	Yes†	84.36	15.64	<0.001
	No	74.58	25.42	
Education	>Secondary school †	78.72	21.28	0.660
	≤Secondary school	77.87	22.13	
Smoking status	No/former †	77.74	22.26	0.137
	Current smoker	76.27	23.73	
Alcohol status	No/former †	74.15	25.85	0.155
	Current drinker	77..6	22.4	

† Reference value; BMI, body mass index; CAD, Canadian dollars; $p \leq 0.05$.

A lower prevalence of CDs was observed among Chinese, Blacks, Filipinos, Arabs, and the "all other ethnicities" group compared with the white group (Table A2). The prevalence of CDs based on region and place of birth is presented in Table A3. Those born in South/Central America, the Caribbean, Africa, and Asia had a lower prevalence of CDs than those born in Canada and North America. A detailed analysis based on the country of birth showed that, compared with native-born Canadians, more participants born in Italy had CDs and fewer of those born in the Philippines had CDs.

Compared with non-immigrants, immigrants had a lower prevalence of heart disease, cancer, asthma, inflammatory lung diseases, and CDs but a higher prevalence of vitD insufficiency (52.82 vs. 31.75, $P < 0.001$). Immigrants also had lower mean concentration levels of S-25(OH)D, serum hs-CRP, and Hb and higher mean levels of HbA1c, the TC/HDL ratio, and ferritin than non-immigrants (Table 2).

Table 2. Weighted prevalence of chronic diseases, chronic-disease-related biomarkers, and self-rated general and mental health by immigration status.

		Non-Immigrants † (78.1%), %	Immigrants (21.9%), %	All participants, (100%), %	P-value
Diabetes	(Yes)	4.82	6.59	5.21	0.095
Heart disease	(Yes)	3.55	2.37	3.29	0.029
Cancer	(Yes)	6.41	4.65	6.02	0.041
Asthma	(Yes)	11.46	5.06	10.05	<0.001
Inflammatory lung diseases [a]	(Yes)	3.86	1.95	3.34	0.028
CDs [b]	(Yes)	23.2	16.64	21.72	<0.001
Self-rated general health	(Poor/fair)	9.67	11.67	10.11	0.121
Self-rated mental health	(Poor/fair)	8.31	6.76	7.95	0.334
S-25(OH)D, nmol/L	<50	31.75	52.82	36.34	<0.001
CD-Related Biomarkers		**Non-Immigrants † Mean (SE)**	**Immigrants Mean (SE)**	**95% CI**	**P-value**
Serum vitD	S-25(OH)D (nmol/L)	62.72 (1.73)	51.23 (1.41)	8.37, 14.62	<0.001
Glucose homeostasis	HbA1c (%)	5.39 (0.03)	5.52 (0.04)	−0.19, −0.07	<0.001
Lipid profile	TC/HDL ratio	3.63 (0.035)	3.79 (0.07)	−0.30, −0.02	0.030
Immune system and inflammation	hs-CRP (mg/L)	2.46 (0.07)	2.12 (0.13)	0.06, 0.6	0.017
	IgE (IU/mL)	118.37 (6.46)	102.75 (6.59)	−1.14, 32.38	0.066
Hematology	Ferritin (µg/L)	103.07 (2.42)	123.07 (6.20)	−34.45, −5.54	0.009
	Hb (g/L)	140.54 (0.43)	137.73 (0.70)	1.22, 4.42	0.001

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age > 29 years); [b] CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). † Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

Immigrants with diabetes, heart disease, and poor/fair self-reported general and mental health had lower S-25(OH)D levels than non-immigrants. More immigrants with diabetes, heart disease, cancer, asthma, inflammatory lung diseases, CDs, and poor/fair general or mental health had insufficient vitD levels compared with non-immigrants. However, there was no difference in vitD supplement use for any health indicators between immigrants and non-immigrants (Table 3).

Table 3. Weighted mean 25(OH)D (nmol/L), prevalence of vitD insufficiency (<50 nmol/L), and vitD supplement use by immigration status.

	S-25(OH)D (nmol/L)				<50 (nmol/L)			vitD Supplement Use		
	Non-mmigrant Mean (SE)	Immigrant Mean (SE)	95% CI	P-value	Non-Immigrant †%	Immigrant %	P-value	Non-Immigrant †%	Immigrant %	P-value
Diabetes	65.30 (4.05)	47.56 (4.46)	−31.35, −4.13	0.013	31.43	61.63	<0.001	5.28	6.31	0.642
Heart disease	66.63 (2.15)	57.87 (3.80)	−17.42, −0.11	0.048	32.12	38.38	<0.001	[c]	[c]	
Cancer	70.71 (2.86)	67.96 (5.71)	−16.49, 10.98	0.681	29.08	32.28	<0.001	5.02	8.14	0.083
Asthma	59.13 (2.37)	54.23 (3.36)	−12.97, 3.18	0.222	30.68	53.59	<0.001	[c]	[c]	
Inflammatory lung diseases [a]	63.87 (1.80)	53.27 (5.80)	−22.09, 0.88	0.069	30.76	3841	<0.001	[c]	[c]	
CDs [b]	62.18 (1.80)	56.29 (2.49)	−11.23, −0.53	0.033	31.35	47.38	<0.001	4.91	4.97	0.379
Self-rated general health (poor/fair)	58.69 (1.94)	48.68 (2.98)	3.61, 16.43	0.004	31.13	61.2	<0.001	5.28	4.37	0.807
Self-rated mental health (poor/fair)	59.83 (2.43)	47.55 (3.75)	4.12, 20.45	0.005	32.52	64.39	<0.001	5.67	3.67	0.271

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age > 29 years). [b] CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). [c] Data are not sufficient for analysis. [†] Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

There were no differences in S-25(OH)D levels between patients diagnosed before and after immigration for these health indicators (Table 4). There were no dates of diagnosis for inflammatory lung diseases, CDs, and self-reported general and mental health.

Table 4. Weighted mean S-25(OH)D (nmol/L) based on the time of diagnosis (before or after immigration).

	S-25(OH)D, nmol/L			
	Before Immigration † Mean (SE)	**After Immigration Mean (SE)**	**95% CI**	**P-value**
Diabetes	41.80 (3.87)	48.48 (5.31)	−20.59, 7.24	0.331
Heart disease	44.38 (8.01)	59.55 (4.346)	−35.52, 5.18	0.136
Cancer	71.37 (16.93)	67.8 (5.95)	−36.74, 43.80	0.858
Asthma	52.82 (5.88)	56.57 (4.63)	−18.74, 11.25	0.609

† Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

The results shown in Appendix A and Tables A4–A7 represent all study participants and are not stratified by immigration status or CDs. No differences were observed in mean S-25(OH)D levels by recent or long-term diagnosis (Table A4). The data were not analyzed for inflammatory lung diseases, CDs, and self-reported general and mental health because the date of diagnosis was not given.

The mean values for S-25(OH)D, vitD status (sufficiency/insufficiency), and the use of vitD supplements for each health indicator, including CDs, are presented in Table A5. Patients diagnosed with diabetes had insufficient vitD compared with those without diabetes. Patients with heart disease, CDs, and who self-reported poor/fair general health had higher S-25(OH)D levels than their counterparts without heart disease or CDs and with good general health. Patients with cancer tended to use more supplements than those without cancer. In addition, the mean concentration levels of S-25(OH)D, HbA1c, and IgE were higher among patients with CDs than among those without CDs (Table A6).

The linear regression analysis showed that when the concentration levels of S-25(OH)D increased by 1 nmol/L, HbA1c, the TC/HDL ratio, IgE, ferritin, and Hb decreased (Table A7). In the

multivariable logistic regression analysis, S-25(OH)D was associated with the prevalence of CDs (unadjusted OR: 1.006; 95%CI: 1.00, 1.01; p = 0.007) (result not shown). After adjusting for covariates (Table 5), the final model indicated there was no association between S-25(OH)D and CDs (OR: 1.007; 95%CI: 1.00, 1.01; p = 0.070). Immigrants were healthier (OR for CDs decreased by 60%) than non-immigrants. We also found that when age increased by 1 year, the OR for CDs increased by 2%. The OR increased by 71% among obese participants, by 174% when the HbA1c increased by 1%, and by 0.001% when IgE increased by 1 IU/mL.

Table 5. Multivariable logistic regression analysis for chronic diseases and serum 25(OH)D (contentious) in a predefined model.

		CDs		
		OR (SE)	**95% CI**	**P-value**
S-25(OH)D, nmol/L	1 nmol/L	1.007 (0.004)	1.00, 1.01	0.070
Immigration status	Immigrants	0.40 (0.09)	0.25, 0.63	<0.001
Age, years	1 year	1.02 (0.008)	1.00, 1.04	0.024
Sex	Female	0.86 (0.18)	0.56, 1.33	0.494
Household income, CAD (reference < 50,000)	50,000–100,000	0.61 (0.11)	0.42, 0.88	0.011
	≥100,000	0.56 (0.15)	0.32, 0.99	0.046
Ethnic group	Non-white	1.00 (0.29)	0.54, 1.86	0.998
BMI, kg/m^2 (reference normal weight)	Obese	1.92 (0.47)	1.15, 3.20	0.014
Met physical activity recommendations	No	0.80 (0.21)	0.46, 1.38	0.408
Education	≤Secondary school	0.97 (0.19)	0.69, 1.39	0.841
Smoking status	Current smoker	1.45 (0.34)	0.89, 2.36	0.126
Alcohol	Current drinker	0.64 (0.17)	0.37, 1.12	0.114
VitD supplement or analog use	Yes	0.83 (0.25)	0.45, 1.54	0.540
HbA1c (%)	1%	2.63 (0.37)	1.96, 3.51	<0.001
IgE (IU/mL)	1 IU/mL	1.01 (0.00)	1.00, 1.001	0.001
TC/HDL ratio	Ratio	0.98 (0.10)	0.80, 1.21	0.843
hs-CRP mg/L	1 mg/L	1.01 (0.04)	0.92, 1.10	0.889
Ferritin (µg/L)	1 µg/L	1.00 (0.00)	1.00, 1.001	0.380
Hb (g/L)	1 g/L	0.98 (0.01)	0.97, 1.00	0.060
Constant		0.005 (0.01)	0.000, 0.10	0.001

CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). Adjusted for immigration status, age, sex, household income, education, ethnicity, BMI, physical activity, smoking behavior, alcohol consumption, vitD supplement use, HbA1c (glycated hemoglobin), TC/HDL-R (total cholesterol/high-density lipoprotein cholesterol ratio), Hb (hemoglobin), ferritin, IgE (immunoglobulin E), and hs-CRP (high-sensitivity C-reactive protein).

4. Discussion

This study used data for a large population of native-born Canadians and immigrants from 153 countries. Immigrants had a lower prevalence of CDs than native-born Canadians, including heart disease, cancer, asthma, and inflammatory lung diseases. Immigrants who came to Canada aged ≥18 years had more CDs than those younger than 18 years. There was no difference in the prevalence of CDs before immigration compared with post immigration. However, using two different time points (5 and 10 years), we found that the longer immigrants had lived in Canada, the higher the prevalence of CDs, which may be considered an early sign of health deterioration. Although the CHMS used a cross-sectional design, we used proxy indicators to verify the existence of the healthy immigrant effect (immigrants' health advantage in Canada).

Our results were consistent with those of Vang et al. (2015) who conducted a systematic review involving 77 studies of migration and health in Canada. That study found the healthy immigrant effect was more noticeable among recent immigrants and gradually disappeared among immigrants that were well-established in the host country. Moreover, the advantage of the healthy immigrant effect was also found in terms of protecting immigrants against CDs, including cancer, diabetes, heart disease, asthma, and obesity [6]. Those authors indicated there was a significant deviation for morbidity over time in the healthy immigrant effect, and there were no identifiable underlying reasons for health deterioration [6]. Moreover, Paszat et al. (2017) found that immigration was a determinant for developing colorectal cancer after the first 10 years of arrival in Canada [33]. Another study reported that Canadian immigrants demonstrated lower cancer-specific mortality, but this benefit diminished over time. After adjusting for age, each year following arrival was associated with increased mortality [34].

We hypothesized that lower S-25(OH)D levels, along with environmental and behavioral changes, may explain health deterioration. However, the relationship between vitD and CDs and the acculturation process may be affected by many factors, such as whether immigrants adopted healthy or unhealthy behaviors after immigration compared with before immigration. For example, in previous immigration, acculturation, and vitD studies, it was reported that immigrants less frequently consumed vitD-rich foods, engaged in less physical activity, and were less exposed to sun than non-immigrants [2, 6]. Other studies found the length of residency since immigration was a crucial indicator of lifestyle acculturation. Higher acculturation levels were associated with significantly higher S-25(OH)D [2,5,44].

This study found that, compared with non-immigrants, immigrants had lower mean S-25(OH)D levels and more vitD insufficiency. Similarly, immigrant patients with CDs (e.g., diabetes, heart diseases, cancer, asthma, and inflammatory lung diseases) and poor/fair self-reported general and mental health had higher insufficiency levels than non-immigrants. In a systematic review and meta-analysis of 95 studies (880,128 participants), Chowdhury et al. (2014) reported an inverse association between circulating S-25(OH)D and the risk for death due to cardiovascular disease, cancer, and other mortality causes. Moreover, vitD3 supplementation was inversely associated with lower overall mortality among older adults [11]. Several other studies, including reviews, found that inadequate S-25(OH)D concentration was associated with an increased risk of CDs [20, 21]. Despite the high level of evidence supporting these findings, there remains some controversy regarding the causative nature and efficacy of vitD. For example, there was a two-way correlation between vitD deficiency and disease outcomes such as infectious diseases, rheumatoid arthritis, and obesity [35].

Our previous findings indicated that immigrants had higher S-25(OH)D levels the longer they lived in Canada [2]. To gain better insights about the relationship between the duration of diagnoses and the prevalence of CDs and S-25(OH)D levels, we hypothesized that those who were recently (≤1 year or ≤5 years) diagnosed would have lower S-25(OH)D levels than those with a long duration of diagnosis (>1 year or >5 years). A previous study reported that S-25(OH)D may be sensitive to changes in health status [13]. However, our analysis revealed no difference in S-25(OH)D between recently diagnosed patients and their counterparts with a longer time since diagnosis.

Another study recommended investigating pre-and post-migration experiences to better understand the healthy immigrant effect and health changes over time in the host country [6]. Therefore, we evaluated the prevalence of CDs and pre-and post-immigration vitD by the date of diagnosis and date of immigration. The results showed no differences in mean S-25(OH)D among immigrants diagnosed before immigration compared with those diagnosed after immigration for any of the studied health indicators (diabetes, heart disease, cancer, and asthma).

We assumed that having lower S-25(OH)D levels (deficient or insufficient vitD) for a long time may increase the risk of a CD diagnosis. Therefore, we investigated the relationships between the length of time since immigration and vitD status and CDs. Our results showed that the longer the time after immigration, the higher the prevalence of CDs among immigrants.

Our univariate analyses showed that the mean concentrations of CD-related biomarkers (HbA1c, hs-CRP, and IgE) were higher among patients with CDs compared with those without CDs. We did not expect to find the mean concentration of S-25(OH)D was higher among patients with CDs compared with their non-CD counterparts: mean (SE) 63.118 (1.787) versus 59.42 (1.76) (95%CI: −6.27, −1.13; $p = 0.007$). However, the findings related to immigration status and the use of vitD supplements along with other covariates may change the direction of the relationship between CDs

and S-25(OH)D. For example, non-immigrants had more CDs and higher S-25(OH)D, and patients with CDs used more vitD supplementation than those without CDs. After adjusting for immigration status, vitD supplementation, and other covariates, S-25(OH)D was not associated with CDs, although HbA1c and IgE remained associated with a higher prevalence of CDs.

Our analysis showed a negative association between S-25(OH)D and HbA1c, the TC/HDL ratio, IgE, ferritin, and Hb levels. Using the same data for Canadian adults, another study found the same inverse association between S-25(OH)D and elevated ferritin [36]. In addition, vitD supplementation was found to improve S-25(OH)D levels among patients with diabetes with vitD deficiency [37]. Our investigation of the concentrations of these biomarkers among immigrants compared with non-immigrants showed that immigrants had higher concentrations of HbA1c, and ferritin, a higher TC/HDL ratio, and lower levels of hs-CRP and Hb than non-immigrants. These deviations in CD-related biomarkers may be a preliminary indicator for the decline in the health status of immigrants in the long term.

Our univariate analyses revealed that immigrants with insufficient vitD were more likely to self-report poor/fair general and mental health than non-immigrants. Previous studies hypothesized that low vitD concentration was associated with depression [38, 39]. Another study found that anxiety, depression, and health-related quality of life were not associated with S-25(OH)D levels among the immigrant population [40]. Our analysis revealed that the prevalence of CDs was higher among those with older age, lower household income, and obesity. White ethnic groups had a higher prevalence of CDs than non-white groups, and CDs varied among immigrants from different ethnic groups and countries and regions of birth. Our finding concerning the health advantage of being immigrants (i.e., fewer CDs) was observed among Chinese, Black, Filipino, and Arab ethnicities as well as those born in South/Central America and the Caribbean, Africa, Asia, and the

Philippines. In contrast, this effect was less consistent (i.e., more CDs) for those born in Italy. However, the difference in health status among immigrants may reflect variations in acculturation. The effect of origin in terms of health, life expectancy, and mortality patterns among immigrant populations varies across different ethnic groups [41].

There was no association between S-25(OH)D and CDs in our adjusted regression model. However, in addition to the environmental and lifestyle changes after immigration, we assumed the cumulative impact of immigrants' lower levels of S-25(OH)D and the deviation in CD-related biomarkers over time played a crucial role in the subsequent health deterioration among immigrants in terms of the investigated proxy indicators. Furthermore, we assumed that improving S-25(OH)D over time, as found in our previous analysis [2], did not enhance the deviated biomarkers or cure CDs once they had developed. In a randomized control trial, vitD supplementation for patients with type 2 diabetes and asymptomatic vitD deficiency did not improve HbA1c levels [37].

However, considering the consistency of results related to higher deficiency levels of S-25(OH)D among immigrants and the relatively new findings relating to vitD and health deterioration, we cannot quantify the degree and time of deterioration nor guarantee such an association. Therefore, we recommend further research on this topic using longitudinal designs. Immigrants can be followed over their residency time in the host country to explain the patterns, developments, and direction of health deterioration.

Cross-sectional surveys such as the CHMS are not usually used to examine changes in health over time. The bidirectional association between S-25(OH)D and CDs is complex, and it is challenging to address residual confounding using an observational study design. Longitudinal observation and

interventional trials are warranted to further understand the relationship between S-25(OH)D and immigrants' health deterioration.

A limitation of using secondary data is that some of the chronic diseases could not be included in the analysis because the date of diagnosis was not provided. The CHMS data did not differentiate immigrants by specific immigration class or type (e.g., refugees, family class, economic migrants, or asylum seekers). Moreover, native-born Canadians formed a single group, despite some being second- or third-generation immigrants; this resulted in a high level of heterogeneity in the reference population. Previous immigration studies recommended assessing vitD status and its determinants among subgroups living in the same country [42]. To compare the same generation of immigrants rather than aggregated generations [43], it will be necessary to gather evidence and formulate recommendations specific to sub-populations that may differ from the overall immigrant population [25].

5. Conclusions

This study confirmed that the current health status of immigrants is good (healthy), but over time they may experience more CDs than their non-immigrant counterparts. S-25(OH)D is associated with environmental and behavioral factors and acts as a biological measure but is not associated with immigrants' current health status. However, in addition to the adoption of unhealthy diets and lifestyles, lower levels of accumulated S-25(OH)D may impact the health profile of immigrants in terms of CD-related biomarkers. This may partially explain immigrants' health deterioration over time. Given the emerging research interest in immigrants' health deterioration, we recommend further longitudinal research to investigate the relationship between vitD and health deterioration, accounting for the dietary and lifestyle acculturation process.

Author Contributions: SY and GW conceived this study. With close supervision from GW, SY managed the data, verified the analytical methods, and prepared the tables and figures. AH verified the underlying data at the Research Data Center. SY interpreted the results and prepared the final draft. All authors including IC, MP, DM, and MF, contributed to the design and analysis of the research, and the substantive review of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025). The Health Canada Research Ethics Board approved the CHMS.

Informed Consent Statement: Statistics Canada collected written consent from all participants for a personal interview, physical measures, and biospecimens collection.

Data Availability Statement: Data described in the manuscript, codebook, and analytic codes are not publicly available because the data are confidential national data hosted by Statistics Canada.

Acknowledgments: The authors acknowledge the Carleton, Ottawa, Outaouais Local Research Data Centre team for assistance with access to CHMS data. CHMS data were obtained and supported by funding to the Canadian Research Data Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. Although the research and analysis were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Conflicts of Interest: The authors declare no personal or financial conflicts of interest.

References (Main manuscript 3.3)

1. Gushulak, B.D. and L.S. Williams, *National Immigration Health Policy Existing Policy, Changing Needs, and Future Directions.* CANADIAN JOURNAL OF PUBLIC HEALTH, 2004. **95**(3): p. 1-27.
2. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.
3. Statistics Canada. *Population Projections for Canada, provinces and Territories*. 2014 [cited 2021 20/11/2021]; Available from: https://www150.statcan.gc.ca/n1/en/pub/91-520-x/91-520-x2010001-eng.pdf?st=LWFifucU.
4. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
5. Sanou, D., et al., *Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.
6. Vang, Z., et al., *The Healthy Immigrant Effect in Canada: A Systematic Review.* Population Change and Lifecourse Strategic Knowledge Cluster Discussion Paper Series/Un Réseau stratégique de connaissances Changements de population et parcours de vie Document de travail 2015. **3**(1): p. 4.
7. Autier, P., *Vitamin D status as a synthetic biomarker of health status.* Endocrine, 2016. **51**(2): p. 201-202.
8. Chiu, M., et al., *Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-ethnic Study.* Canadian Journal of Cardiology, 2012. **28**(1): p. 20-26.
9. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.
10. Williams, D.R., et al., *Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities.* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 69-101.
11. Chowdhury, R., et al., *Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies.* Bmj, 2014. 348.
12. Holick, M.F., *The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health INTRODUCTION: HISTORICAL PERSPECTIVE.* Public Health Reviews, 2010. 32(1): p. 267-283.
13. McNeill, G., et al., *Predictors of micronutrient status in men and women over 75 years old living in the community.* British journal of nutrition, 2002. 88(5): p. 555-561.
14. Sun, Y.-Q., et al., *Serum 25-hydroxyvitamin D level, chronic diseases and all-cause mortality in a population-based prospective cohort: the HUNT Study, Norway.* BMJ open, 2017. **7**(6): p. e017256.

15. Jablonski, N.G. and G. Chaplin, *Human skin pigmentation, migration and disease susceptibility.* Philosophical Transactions of the Royal Society B: Biological Sciences, 2012. 367(1590): p. 785-792.

16. Heaney, R.P. and M.F. Holick, *Why the IOM recommendations for vitamin D are deficient.* Journal of Bone and Mineral Research, 2011. 26(3): p. 455-457.

17. Pham, T., *Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal.* Thesis-McGill University, 2012.

18. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. 39(4): p. 322-350.

19. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D,* in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.

20. Peterlik, M., et al., *Vitamin D and calcium insufficiency-related chronic diseases: an emerging world-wide public health problem.* International journal of environmental research and public health, 2009. 6(10): p. 2585-2607.

21. Renzaho, A.M.N., J.A. Halliday Bhsci, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review.* Nutrition, 2011. **27**: p. 868-879.

22. Cristian Ilie, P., S. Stefanescu, and L. Smith, *The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality.* Aging clinical and experimental research 2020. **32**(7): p. 1195-1198.

23. Ghasemian, R., et al., *The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis.* medRxiv, 2021: p. 2020.06.05.20123554-2020.06.05.20123554.

24. Mercola, J., W.B. Grant, and C.L. Wagner, *Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity.* Nutrients, 2020. **12**(11): p. 3361-3361.

25. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis.* Systematic Reviews, 2019. **8**(1): p. 1-6.

26. Levinsky, M. and M. Schiff, *Lifetime cumulative adversity and physical health deterioration in old age: Evidence from a fourteen-year longitudinal study.* Social Science & Medicine, 2021. **289**: p. 114407.

27. Thacker, S.B., et al., *Measuring the public's health.* Public health reports, 2006. **121**(1): p. 14-22.

28. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*.* Bulletin of the World Health Organization, 2007. **85**(11): p. 867-872.

29. Day, B., et al., *Canadian Health Measures Survey: ethical, legal and social issues,* in *Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé*. 2007. p. 37-51.

30. Ng, E., *Canadian Health Measures Survey: A tool for immigrant health research?* Statistics Canada, Health Report, 2015.

31. StatisticsCanada. *Canadian Health Measures Survey, Cycle 3, Privacy impact assessment* 2012-2013; Available from: https://www.statcan.gc.ca/eng/about/pia/chmsc3.

32. Statistics Canada, *Canadian Health Measures Survey, Cycle 4, 2014-2015 - Privacy impact assessment summary*. 2014-2015.

33. Paszat, L., et al., *Risk of colorectal cancer among immigrants to Ontario, Canada.* BMC gastroenterology, 2017. **17**(1): p. 1-11.

34. Cheung, M.C., et al., *Impact of immigration status on cancer outcomes in Ontario, Canada.* Journal of Oncology Practice, 2017. **13**(7): p. e602-e612.

35. Spedding-Simon, *Vitamin D and Human Health*. 2015 ed. 2015, MDPI • Basel • Beijing • Wuhan: Publisher Shu-Kun Lin.

36. Munasinghe, L.L., et al., *The association of serum 25-hydroxyvitamin D concentrations with elevated serum ferritin levels in normal weight, overweight and obese Canadians.* PLoS One, 2019. **14**(3): p. e0213260.

37. Randhawa, F.A., et al., *Effect of Vitamin D supplementation on reduction in levels of HbA1 in patients recently diagnosed with type 2 Diabetes Mellitus having asymptomatic Vitamin D deficiency.* Pakistan journal of medical sciences, 2017. **33**(4): p. 881.

38. Anglin, R.E., et al., *Vitamin D deficiency and depression in adults: systematic review and meta-analysis.* The British journal of psychiatry, 2013. **202**(2): p. 100-107.

39. Chu, F., et al., *Serum 25-Hydroxyvitamin D Concentrations and Indicators of Mental Health: An Analysis of the Canadian Health Measures Survey.* Nutrients, 2017. **9**(10): p. 1116-1116.

40. Granlund, L.E., et al., *Vitamin D status was not associated with anxiety, depression, or health-related quality of life in Middle Eastern and African-born immigrants in Sweden.* Nutrition Research, 2020. **75**: p. 109-118.

41. Huh, J., J.A. Prause, and C.D. Dooley, *The impact of nativity on chronic diseases, self-rated health and comorbidity status of Asian and Hispanic immigrants.* Journal of immigrant and minority health, 2008. **10**(2): p. 103-118.

42. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British Journal of Nutrition, 2014. **111**: p. 23-45.

43. Zhu, L., *Depression risks and correlates among different generations of Chinese Americans: The effects of relationships with friends and relatives.* Social Sciences, 2017. **6**(2).

Supporting material

Appendix A: Supporting information, including (Tables A1–A7).

Table A1. Biomarker details

Biomarkers	*Symbol*	*Unit*	*Method of measurements/name of the machine and related information*	*Analytical detection limit*	*CHMS reference laboratory precision target*
Serum 25-hydroxyvitamin D [1, 2]	*S-25(OH)D*	*nmol/L*	Chemiluminescent immunoassay technology (DiaSorin, Ltd, Stillwater, Minnesota)	10–375	<20 nmol/L = 15% 20–100 nmol/L = 10% >100 nmol/L = 12%
Glycated hemoglobin	*HbA1c*	*%*	Immunoturbidimetric end-point spectrophotometry (anti-HbA1c antibody, polyhapten) on the Ortho Clinical Diagnostics Vitros 5,1FS analyzer. %A1c is a derived test calculated from the quantitative measurements of hemoglobin and hemoglobin A1c	Hb: 6.0–22.0 g/dL(component) HbA1c: 0.2–2.5 g/dL (component) %A1c: 4%–14% NGSP	5%
Total cholesterol/HDL cholesterol ratio	*TC/HDL-ratio*		Derived – calculation	N/A	N/A
High sensitivity C-reactive protein	*hs-CRP*	*mg/L*	Immunoturbidimetric two-point rate reflectance spectrophotometry (monoclonal antibodies) on the Ortho Clinical Diagnostics Vitros 5,1FS analyzer	0.10–15.0	5%
Total immunoglobulin E	*IgE*	*IU/mL*	Two-site sandwich immunoassay using direct chemiluminescent technology on the Siemens ADVIA Centaur XP analyzer	1.5–3300	10%
Ferritin	*Ferritin*	*µg/L*	Two-site sandwich immunoassay using direct chemiluminescent technology on the Siemens ADVIA Centaur XP analyzer	0.5–1650	10%
Hemoglobin	*Hb*	*g/L*	Hemoglobin is a non-cyanide-based method read photometrically at 555 nm on the POCH-i100 Sysmex hematology analyzer	0–25.0	1.5%

Table A2. Weighted prevalence of chronic diseases by ethnicity

	No CDs (78.3%), %	**CDs (21.7%), %**	**P-value**
White †	76.72	23.28	-
Aboriginal	74.47	25.53	0.446
South Asian	80.85	19.15	0.309
Chinese	86.08	13.92	0.014
Black	89.33	10.67	0.002
Filipino	89.77	10.23	0.011
Latin American	86.48	13.52	0.155
Arab	88.92	11.08	0.049
Southeast Asian	83.78	16.22	0.137
West Asian	90.89	9.11	0.196
Japanese	60.2	39.8	0.141
Multiple ethnicities	72.13	27.87	0.250
Other ethnicities	84.05	15.95	<0.001

CDs (chronic diseases): at least one of the lists CDs (diabetes; heart disease; cancer; asthma; inflammatory lung diseases).

† Reference value; $P \leq 0.05$.

Data for Koreans were insufficient for analysis.

Table A3. Weighted prevalence of chronic diseases by country and region of birth

		No CDs (78.3%), %	CDs (21.7%), %	P-value
Region of birth	Canada and North America †	76.53	23.47	-
	South/Central America and the Caribbean	86.75	13.25	0.011
	Europe	78.96	21.04	0.314
	Africa	88.74	11.26	0.008
	Asia	85.94	14.06	0.006
Country of birth	Canada †	76.39	23.61	-
	China	80.81	19.19	0.575
	USA	84.31	15.69	0.224
	France	89.7	10.3	0.066
	Jamaica	81.21	18.79	0.648
	UK	72.97	27.03	0.397
	Mexico	81.54	18.46	0.527
	Netherlands	60.97	39.03	0.155
	India	82.51	17.49	0.115
	Philippines	94.64	5.36	<0.001
	Hong Kong	77.8	22.2	0.907
	Germany	72.55	27.45	0.625
	Italy	53.56	46.44	0.004
	Iran	84.93	15.07	0.537
	Lebanon	49.67	50.33	0.126
	Others	87.37	12.63	<0.001

CDs (chronic diseases): at least one of the listed CDs (diabetes; heart disease; cancer; asthma; inflammatory lung diseases)

† Reference value; $P \leq 0.05$.

The data for Algeria, Pakistan, Romania, Colombia, and Morocco were insufficient for analysis.

Table A4. Weighted mean 25(OH)D for each chronic disease based on the date of diagnosis: recent (e.g., ≤1 year) versus long-term (e.g., >1 year)

	S-25(OH)D, nmol/L											
	Diagnosis ≤1 year †		Diagnosis >1 year				Diagnosis ≤5 years †		Diagnosis >5 years			
	%	Mean (SE)	%	Mean (SE)	95% CI	P-value	%	Mean (SE)	%	Mean (SE)	(95% CI)	P-value
Diabetes	9.47	45.63 (10.28)	90.53	62.58 (3.16)	−38.21, 4.31	0.113	61.8	64.80 6.41)	38.92	58.52 (3.15)	−8.07, 20.62	0.374
Heart disease	7.17	58.00 (5.97)	92.83	65.80 (1.98)	−20.58, 4.99	0.220	69.32	63.19 (2.58)	30.68	66.14 (2.04)	−7.78, 1.88	0.218
Cancer	11.78	75.47 (3.82)	88.22	69.55 (2.68)	−2.93, 14.76	0.179	59.76	66.89 (3.82)	40.24	72.44 (3.34)	−16.57, 5.47	0.308
Asthma	3.56	61.17 (4.50)	96.44	57.82 (2.34)	−5.19, 11.89	0.425	83.21	61.12 (2.78)	16.79	57.31 (2.43)	−1.19, 8.81	0.129

† Reference value; $P \leq 0.05$; SE, standard error; CI, confidence interval

Table A5. Weighted mean and status of 25(OH)D for each chronic disease and the use of vitD supplements

		25(OH)D, nmol/L			S-25(OH)D status			VitD supplements		
		Mean (SE)	**95% CI**	**P-value**	**≥50 nmol/L, %**	**<50 nmol/L, %**	**P-value**	**No, %**	**Yes, %**	**P-value**
Diabetes	No †	60.23 (1.66)			64.14	35.86		94.84	5.16	
	Yes	60.32 (3.15)	−5.08, 4.89	0.968	55.11	44.89	0.043	92.6	7.54	0.142
Heart disease	No †	60.04 (1.72)			63.24	36.76		94.92	5.08	
	Yes	65.21 (1.94)	−9.42, −0.91	0.020	75.78	24.22	0.005	88.56	11.44	0.102
Cancer	No †	59.51 (1.78)			62.84	37.16		95.04	4.96	
	Yes	70.23 (2.46)	−16.44, −4.99	0.001	74.76	25.24	0.068	89.06	10.94	0.025
Asthma	No †	60.40 (1.69)			64.22	35..78		94.51	5.49	
	Yes	58.57 (2.20)	−1.02, 4.68	0.197	58.68	41.32	0.095	96.80	3.20	0.104
Inflammatory lung diseases a	No †	60.90 (1.70)			64.11	35.89		92.80	7.20	
	Yes	61.74 (2.38)	−5.03, 3.36	0.685	61.92	38..08	0.538	84.99	15.01	0.161
CDs b	No CDs †	59.41(1.76)			63.41	36.59		95.11	4.89	
	CDs	63.11(1.79)	−6.27, −1.13	0.007	64.59	35.41	0.5945	93.19	6.81	0.119
Self-rated general health	Good †	56.35 (2.01)			64.4	35.6		94.81	51.9	
	Poor/Fair	60.66 (1.73)	1.10, 7.52	0.011	56.98	43.02	0.023	94.00	6.00	0.479
Self-rated mental health	Good †	57.33 (2.24)			62.89	37.11		94.45	5.55	
	Poor/Fair	59.10 (1.70)	−1.11, 6.44	0.157	56.51	43.49	0.197	91.61	8.39	0.401

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age >29 years)

[b] CDs (chronic diseases): at least one of the listed CDs (diabetes; heart disease; cancer; asthma; inflammatory lung diseases)

† Reference value; $P \leq 0.05$; SE, standard error; CI, confidence interval; Good = Excellent/Very Good/Good; <50 = Insufficient; ≥50 = Sufficient

Table A6. Weighted means for biomarkers by the presence of chronic diseases

		Chronic diseases (CDs)			
		No CDs † Mean (SE)	**CDs Mean (SE)**	**95%CI**	**P-value**
Serum vitD	*S-25(OH)D, nmol/L*	59.42 (1.76)	63.118 (1.787)	−6.27, −1.13	0.007
Glucose homeostasis	*HbA1c, %*	5.30 (0.2)	5.82 (0.05)	−0.62, −0.41	<0.001
Lipid profile	*TC/HDL-ratio*	3.65 (0.03)	3.72 (0.07)	−0.20, 0.07	0.309
Immune system and inflammation	*hs-CRP, mg/L*	2.22 (0.08)	2.91 (0.14)	−1.03, −0.35	<0.001
	IgE, IU/mL	95.48 (5.85)	181.74 (20.96)	−134.29, −38.23	0.001
Hematology	*Ferritin, µg/L*	106.02 (2.57)	114.90 (5.02)	−20.95, 3.19	0.141
	Hb, g/L	139.84 (042)	140.22 (0.74)	−1.86, 1.12	0.609

† Reference value; $P \leq 0.05$; CDs, chronic diseases; SE, standard error; CI, confidence interval.

Table A7. Linear regression of S-25(OH)D and chronic disease-related biomarkers

		S-25(OH)D and CD-related biomarkers			
		Mean (SE)	**β (SE)**	**95%CI**	**P-value**
Serum vitD	*S-25(OH)D, nmol/L*	60.22 (1.69)	-	-	-
Glucose homeostasis	*HbA1c, %*	5.42 (0.03)	−1.79 (0.79)	−3.43, −0.142	0.035
Lipid profile	*TC/HDL-ratio*	3.67 (0.03)	−4.09 (0.39)	−4.90, −3.28	<0.001
Immune system and inflammation	*hs-CRP, mg/L*	2.38 (0.07)	−0.50 (0.23)	−0.94, 0.02	0.058
	IgE, IU/mL	114.6 (5.55)	−0.01 (0.00)	−0.01, −0.00	0.007
Hematology	*Ferritin, µg/L*	108.05 (2.18)	−0.02 (0.00)	−0.03, −0.01	0.003
	Hb, g/L	139.93 (0.41)	−0.10 (0.04)	−0.19, −0.02	0.016

$P \leq 0.05$; SE, standard error; CI, confidence interval; CD, chronic disease.

References (Appendices 3.3)

1. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.
2. Munasinghe, L.L., et al., *Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010.* British Journal of Nutrition, 2017. **117**: p. 457-465.

Chapter 4: Quality and content of clinical practice guidelines for vitamin D and for immigrants

Chapter overview

Chapter 4 includes two manuscripts for a systematic review, a protocol, and a full systematic review (Section 4.1, 4.2). Chapter 4 focus on the most recent CPGs pertaining to vitD and to immigrants' health. The chapter addresses the second research question/s: Are the current CPGs acknowledge the pandemic of vitD deficiency among immigrants? Are these CPGs followed the development criteria of guidelines?

Chapter contents

Section 4.1 presents the protocol for the systematic review. This manuscript was published in *Systematic Reviews.*

Section 4.2 describes the results of a systematic review related to the quality and content of clinical practice guidelines for vitD and for immigrants. This manuscript has been submitted for Publication.

A brief description of each manuscript is below, and a detailed description is given on the first page of each section.

4.1 Study protocol: Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: a systematic review

Section overview

This section presents a manuscript describing the protocol for a systematic review. This protocol was registered with PROSPERO (CRD42021240562) in 2021 and published in 2022. The protocol highlighted the topic background, search strategy and other methodological aspects, and a brief rational for the systematic review.

Manuscript status

This manuscript has been published in *systematic Reviews;* doi.org/10.1186/s13643-022-02129-6

Yousef S, Hayawi L, Manuel M, Colman I, Papadimitropoulos M, Hossain A, Faris M, Wells G. A,

Author roles and contributions

YS, HL, MD, CI, PM, HA, FM, and GW conceived this study. YS designed and will execute the search strategy. YS, and HL will screen, select studies for inclusion, and perform data extraction. YS drafted the protocol, which was revised by all authors. All authors approved the version of the manuscript submitted for publication.

Related thesis appendices

Appendix A4:

The PDF of the PROSPERO (CRD42021240562) registration Appendix A4.1.

The PDF of the published protocol is presented in Appendix A4.2.

Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: A protocol for systematic review

Said Yousef*; Lamia Hayawi; Douglas Manuel; Ian Colman; Manny Papadimitropoulos;

Alomgir Hossain; MoezAlIslam Faris; George A Wells

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Lamia Hayawi, MD, MSc
Children's Hospital of Eastern Ontario Research Institute,
Ottawa, ON, Canada
lhayawi@cheo.on.ca

Douglas Manuel, MD, MSc.
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Introduction: Worldwide, more immigrants experience vitamin D (vitD) deficiency than non-immigrants, which is attributed to ethnic variations, place or region of birth, skin pigmentation, clothing style, and resettlement-related changes in diet, physical activity, and sun exposure. Current recommendations in clinical practice guidelines (CPGs) concerning vitD are inadequate to address vitD deficiency among immigrants. CPGs may also lack guidance for physicians on vitD supplementation for immigrants. Moreover, there are concerns about the overall quality of these CPGs.

Objectives: This systematic review will collate and critically appraise CPGs relevant to immigrants' health and vitD. Moreover, we will evaluate whether the CPGs of vitD include recommendations for immigrants and clarify whether the CPGs of immigrants include recommendations on vitD.

Methods: A systematic search of Ovid MEDLINE® ALL, EMBASE, and Turning Research Into Practice (TRIP) electronic databases, guideline repositories, and grey literature will be conducted to identify relevant CPGs. Two reviewers will independently evaluate the methodological quality of the retrieved guidelines using the Appraisal of Guidelines, Research, and Evaluation-II (AGREE-II) instrument. CPGs scoring ≥60% in at least four domains, including "rigor of development," will be considered high quality.

Conclusion: Evaluating the quality and content of relevant CPGs may support researchers in developing national and global guidelines for immigrants. Furthermore, it may support vitD testing, nutritional counseling, and supplementation for vulnerable immigrant sub-populations.

PROSPERO registration number: CRD42021240562

Keywords: Vitamin D, Clinical practice guideline, Immigrants; AGREE-II

Introduction

Globally, immigrant populations represent diverse categories including economic migrants, family members, refugees, and asylum [1, 2]. Immigrants' health status after immigration remains an important area of concern [3]. Studies have shown that immigrants' physical and mental health declines quickly after arrival to their host countries [1, 4-6], and further health changes can occur over 5–10 years [4, 7]. Recent migrants are reported to have better health compared with people of the host country, including long-term migrants who had migrated to the host country at an earlier time; this phenomenon is called the "healthy immigrant effect" [8]. It has been hypothesized that the healthy immigrant effect results from a combination of pre- and post-migration factors. Pre-migration factors include biased and rigorous selection criteria that favor immigrants that are healthier, wealthier, and better educated than the general population in the country of origin [8, 9]. In addition, decline in immigrants' health status after arrival may be explained by psychosocial factors and lifestyle changes [1, 9-11]. The mechanisms underlying this health decline in immigrants have not been explicitly identified [1, 4]. However, the healthy immigrant effect appears to decline over time when immigrants are exposed to their new environment [5]. Evidence also suggests that immigrants have lower vitD compared with native-born populations [12-14]. In a recent national large-scale Canadian data, Yousef et al. 2021, found ethnicity was the factor most strongly associated with serum vitD status among immigrants from 153 countries and more than 13 ethnicities [14]. Moreover, vitD status varies among immigrants because of skin pigmentation, clothing, place or region of birth, and resettlement changes in diet, physical activity, and sun exposure [12, 14-16].

The Institute of Medicine (IOM) defines clinical practice guidelines (CPGs) as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [17]. The main purposes of CPGs are to improve the effectiveness and quality of care and decrease variations in healthcare practices based on scientific evidence [17, 18]. Worldwide, more CPGs covering immigrants' health have become available in the last two decades, with the main focus areas being screening, treatment, immunization, infectious diseases, mental health, and chronic diseases [2, 19, 20]. The Canadian Immigrant and Refugee Guideline refer to the first 5 years of immigration to Canada as the time during which the healthy immigrant effect begins to decline. However, the developers of this guideline highlighted the topic of vitD deficiency among immigrants as an emerging condition that was not emphasized in their guidelines [20].

CPGs covering vitD that are currently available vary among countries and professional development organizations in terms of the scope, targeted population, and recommendations [21] [21-24]. Notably, the current recommendations for vitD are inadequate to address the growing epidemic of vitD deficiency in immigrant populations [23, 25]. Moreover, the majority of guidelines do not include specific recommendations for different immigrant populations or certain ethnic groups [21, 23, 26, 27].

In addition, concerns have been raised about the overall quality of these CPGs [2, 28, 29]. The Appraisal of Guidelines for Research and Evaluation-II (AGREE-II) instrument has been widely used to assess guideline quality, define the information that needs to be reported, and inform guideline development [30, 31]. The overall guideline assessment includes judgment on the quality of the guideline and whether the guideline would be recommended for use [31]. Previous studies that assessed the quality of CPGs using the AGREE-II instrument were inconsistent in how they

determined high-quality. For example, with inclusion of the "rigor of development" domain, a score of high quality was reported as ≥60% in at least three of the six domains [2], four of the six domains [32], or in all six domains [33].

Research Objectives

This systematic review will focus on the critical appraisal of guidelines relevant to vitD and immigrants' health using the AGREE-II instrument. Moreover, it aims to evaluate the guideline content to clarify whether recommendations for immigrant populations were included in vitD guidelines, and whether vitD recommendations were included in immigrant guidelines.

Research Questions

The appraisal will be based on specific research questions and clarify whether the included CPGs comply with the quality standards of the AGREE-II instrument. The research questions are: "Do immigrant CPGs include recommendations on vitD?" and "Do vitD CPGs include recommendations for immigrants, including refugees and asylum seekers?"

Methods and Study Design

The protocol for this review was registered with PROSPERO (CRD42021240562) [34]. The review procedures will follow the methods outlined in the Cochrane Handbook for Systematic Reviews [35]. This protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) Statement [36]; the checklist is presented in Additional file 1.

Search Strategy

The search strategy used to identify published CPGs covering immigrants and vitD will be developed in consultation with an experienced medical information specialist. The databases searched will include Ovid MEDLINE® ALL and EMBASE. These searches will use a combination of controlled vocabulary (e.g., "VitD," "emigrants and immigrants," "refugees") and keywords (e.g., "vitD," "asylum seeker," "foreigner") and incorporate a CADTH-derived guideline filter. We will also search the Turning Research Into Practice (TRIP) database. In addition, we will search grey literatures for guidelines that were internally produced by governments, organizations, and academic institutions and that publishing is a secondary activity for these organizations. For example, a search in the Guidelines International Network (GIN), Joanna Briggs Institute (JBI), World Health Organization (WHO), Healthcare Research and Quality (AHRQ), and National Institution for Excellence (NICE) will be conducted. Results will be limited to relevant publications between 2010 and the date of the search. Supplemental searching will be performed of the reference lists of identified CPGs to detect other key articles.

Eligibility Criteria

We will include two types of CPGs: those concerning immigrants' health and those concerning vitD. The included guidelines will conform to the IOM definition of CPGs [17], and must have been published in the English language between 2010 and the search date. We will include CPGs that have recommendations intended for healthcare professionals on screening, diagnosis, management, or treatment related to immigrants' health or vitD. No restrictions will be applied in regard to age, sex, or health status. In this review, we will define immigrants as those who move cross-country or are international migrants residing in a destination country, irrespective of legal

status and generation. Therefore, any CPGs that include immigrants as a primary population will be evaluated using the AGREE-II tool. CPGs for vitD that emphasize care for patients who are at risk for vitD deficiency in terms of evaluation, treatment, and prevention will also be evaluated using the AGREE-II tool.

Exclusion Criteria

We will exclude non-English language guidelines or incomplete texts. We will also exclude healthcare guidelines that do not consider immigrants or vitD as the primary objective. Dietary or nutritional guidelines for vitD that are not intended for healthcare practices or that target the general population will also be excluded. Furthermore, we will exclude position and consensus papers as well as any other documents that are not equivalent to guidelines.

Outcomes

The primary outcome of this review will be the quality score of the included CPGs based on the AGREE-II scoring tool. Secondary outcomes will be recommendations on vitD as part of immigrant guidelines and recommendations in vitD guidelines that target immigrants.

Selection of CPGs and Data Extraction

The systematic review software "Covidence" (www.covidence.org) will be used to remove duplicates and screen the titles and abstracts of identified GPGs. We will use the AGREE-II instrument (https://www.agreetrust.org) to evaluate the quality of the included guidelines. This tool comprises 23 items and evaluates six domains: "scope and purpose," "stakeholder involvement," "rigor of development," "clarity of presentation," "applicability," and "editorial independence" [31]. An electronic standardized form will be used to record these data and

individual items will be rated using a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree) [31]. More details are available in the AGREE-II manual [31]. The AGREE-II scoring sheet is presented in Additional file 3.

Two reviewers (SY and LH) will independently follow the inclusion and exclusion criteria to assess the citations for inclusion. Both reviewers will resolve differences in their decisions through discussion. A consultation with a third reviewer will be counted when consensus cannot be reached.

One reviewer (SY) will extract the main characteristics of the included published guidelines, including the title, author(s) name(s), year of publication, country, organization that produced the guideline, and key recommendations related to immigrants in vitD CPGs or vitD in immigrant CPGs. The extracted data will be checked by the second reviewer (LH).

Following application of the inclusion and exclusion criteria, two reviewers (SY and LH) will independently evaluate the methodological quality of the included guidelines. Both reviewers had previous training in using the online AGREE-II, and the resulting study was published [32]. Any disagreements will be resolved by discussion with a third reviewer (MF) to reach consensus. The reviewers will evaluate the content of each CPG and any additional supporting documents that are cited in the published guidelines.

Quality Evaluation and Data Synthesis

The reviewers' decisions on the overall quality of recommendations contained in the guidelines will be based on the context in which the AGREE-II is being used. The mean scores for each AGREE-II domain and the overall quality will be presented. A standardized score for each domain

will be calculated using the formula: ((actual score − minimum score)/(maximum score − minimum score)) × 100% [37].

CPGs that score ≥60% in at least four of the six domains, including the "rigor of development" domain, will be considered high quality [32, 38-40]. The intra-class correlation coefficient (ICC) and 95% confidence intervals will be calculated to assess the overall agreement between the reviewers for each guideline. The ICC will be classified as poor (<0.40), moderate (0.40–0.59), good (0.60–0.74), or excellent (0.75–1.00) based on a previous study [41]. We will analyze and summarize the extracted data in a tabular and narrative format. The characteristics of the identified CPGs including author, year, and country with the title will be presented in a table and quality assessment information like the domain percentage score, the ICC, and the overall quality of each guideline in another table. We will narratively discuss if immigrants or ethnicity was mentioned in the guidelines of VitD. Similarly, we will narratively discuss if vitD D was mentioned in CPGs for immigrants.

Discussion

Current national immigrant health policies only cover fragmented snapshots of global immigrant health. In response to growing issues related to immigrants' health, previous researchers recommended regional or global health-related protection agreements [42, 43]. Furthermore, researchers recommended developing a global immigrant guideline that specifies sub-populations for which the evidence and recommendations may differ from the overall immigrant population [12, 13, 43, 44]. For example, the Endocrine Society guidelines recommend screening African Americans, Hispanic Americans [44, 45], and all refugees for vitD deficiency [45]. In a recent Canadian national survey analysis, Yousef et al. (2021) reported vitD levels among immigrants

from 153 origins and more than 13 ethnic groups. That study reported vitD deficiency attributable to ethnicity or country of birth was 6.6%–62.1%, with the highest deficiency levels in the Japanese, Arab, and Southeast Asian ethnic groups, and among those born in Morocco, India, and Lebanon [14, 15].

In this review, evaluating the quality and reviewing content of the guidelines in terms of the recommendations for vitD and immigrants may support researchers in developing national and global immigrant guidelines. VitD-related recommendations may differ for sub-populations who are at high risk for vitD deficiency. Moreover, this review may also help and guide clinicians to support specific vitD testing, nutritional counseling, and supplementation for vulnerable immigrant sub-groups.

Abbreviations

AGREE-II: Appraisal of Guidelines, Research, and Evaluation II instrument; CPGs: clinical practice guidelines; VitD: vitamin D; IOM: Institute of Medicine; PRISMA- P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol; CADTH: Canadian Agency For Drugs And Technologies In Health; TRIP: Turning Research Into Practice; ICC: intra-class correlation coefficient.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: No conflicts declared by authors.

Funding: No funding was received for this study.

Authors' contributions: YS, HL, MD, CI, PM, HA, FM, and GW conceived this study. YS designed and will execute the search strategy. YS, and HL will screen, select studies for inclusion, and perform data extraction. YS drafted the protocol, which was revised by all authors. All authors approved the version of the manuscript submitted for publication.

Acknowledgements: We thank Sarah Visintini, MLIS (Berkman Library, University of Ottawa Heart Institute), and Becky Skidmore, MLS, Ottawa, ON, for peer review the MEDLINE search strategy.

Supporting material

Additional file 1: (PRISMA-P checklist-Vit D Yousef et al.docx)

PRISMA-P 2015 Checklist [46]. This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

Section/topic		Checklist item	Yes	No
Identification	1a	Identify the report as a protocol of a systematic review	Yes	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		No
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Yes	
Authors			Yes	
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No
Support				
Sources	5a	Indicate sources of financial or other support for the review	Yes	
Sponsor	5b	Provide name for the review funder and/or sponsor		No
Role of sponsor/ funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		No
INTRODUCTION			Yes	
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	
METHODS				
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated		No
STUDY RECORDS				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	
DATA				
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)		No
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)		No
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		No
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Yes	

Additional file 2: Medline search strategy

Medline search strategy. Ovid MEDLINE(R) ALL 1946 to October 14, 2020. Date Run: October 15, 2020

1	exp Vitamin D/
2	vitamin D.tw.
3	exp vitamin d deficiency/
4	((avitaminosis or hypovitaminosis) adj1 (D or D2 or D3)).tw,kf.
5	or/1-4
6	exp "Emigrants and Immigrants"/
7	"Emigration and Immigration"/
8	"Transients and Migrants"/
9	refugees/
10	asylum seeker/
11	(alien? or emigrat* or emigrant? or foreigner? or immigrat* or immigrant? or migrant? or migrate? or migration? or migrating or undocumented worker? or foreign born or refugee? or asylum seeker?).tw.
12	or/6-11
13	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
14	(guideline* or standards or consensus* or recommendat*).ti.
15	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
16	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
17	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
18	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
19	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
20	or/13-19
21	(5 or 12) and 20
22	exp animals/

23	exp animal experimentation/ or exp animal experiment/
24	exp models animal/
25	nonhuman/
26	exp vertebrate/ or exp vertebrates/
27	exp humans/
28	exp human experimentation/ or exp human experiment/
29	or/22-26
30	or/27-28
31	29 not 30
32	21 not 31
33	limit 32 to yr="2010 - 2020"
34	(conference abstract or conference review).pt.
35	33 not 34

Additional file 3: AGREE-II Checklist

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	**2**	**3**	**4**	**5**	**6**	**7** *Strongly Agree*
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.							
	2. The health question(s) covered by the guideline is (are) specifically described.							
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.							
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.							
	5. The views and preferences of the target population (patients, public, etc.) have been sought.							
	6. The target users of the guideline are clearly defined.							
Rigor of development	7. Systematic methods were used to search for evidence.							
	8. The criteria for selecting the evidence are clearly described.							
	9. The strengths and limitations of the body of evidence are clearly described.							
	10. The methods for formulating the recommendations are clearly described.							
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.							
	12. There is an explicit link between the recommendations and the supporting evidence.							
	13. The guideline has been externally reviewed by experts prior to its publication.							
	14. A procedure for updating the guideline is provided.							
Clarity of presentation	15. The recommendations are specific and unambiguous.							
	16. The different options for management of the condition or health issue are clearly presented.							
	17. Key recommendations are easily identifiable.							
Applicability	18. The guideline describes facilitators and barriers to its application.							
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.							
	20. The potential resource implications of applying the recommendations have been considered.							
	21. The guideline presents monitoring and/ or auditing criteria.							
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.							
	23. Competing interests of guideline development group members have been recorded and addressed.							

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	**2**	**3**	**4**	**5**	**6**	**7** *Strongly Agree*
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	1 *Lowest possible quality*	2	3	4	5	6	7 *Highest possible quality*
Overall Guideline Assessment	2. I would recommend this guideline for use.	*Yes*		*Yes, with modifications*				*No*

1 Strongly Disagree; 7 Strongly Agree

References

1. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.
2. Agbata, E.N., et al., *Migrant Healthcare Guidelines: A Systematic Quality Assessment.* Journal of Immigrant and Minority Health, 2019. **21**(2): p. 401-413.
3. Fernando, G.D.M. and K. Eagan, *The deterioration of health status among immigrants to Canada.: EBSCOhost*, in *Vol. 5, No. 5, September 2010, 462478*. 2010. p. 462-478.
4. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
5. Kennedy, S., J.T. McDonald, and N. Biddle, *The Healthy Immigrant Effect and Immigrant Selection: Evidence from Four Countries.* 2006.
6. Hansson, E., et al., *Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement*, in *for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada*. 2010.
7. Newbold, B., *Health status and health care of immigrants in Canada: a longitudinal analysis.* Journal of Health Services Research & Policy Nursing & Allied Health Database 2005. **10**(2).
8. Ichou, M. and M. Wallace, *The Healthy Immigrant Effect: The role of educational selectivity in the good health of migrants.* DEMOGRAPHIC RESEARCH, 2019. **40**: p. 61–94.
9. Chiu, M., et al., *Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-ethnic Study.* Canadian Journal of Cardiology, 2012. **28**(1): p. 20-26.
10. Beiser, M., *The International refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada*. 1993.
11. Williams, D.R., et al., *Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities.* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 69-101.
12. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.
13. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

14. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.

15. Centers for Disease Control Prevention. *Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination. .* 2013; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf.

16. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

17. Graham, R., et al., *Clinical Practice Guidelines We Can Trust*. Clinical Practice Guidelines We Can Trust. 2011.

18. Kredo, T., et al., *Guide to clinical practice guidelines: the current state of play.* International Journal for Quality in Health Care, 2016. **28**(1): p. 122-122.

19. Swinkels H, P.K., Tugwell P, Rashid M, Narasiah L, *Development of guidelines for recently arrived immigrants and refugees to Canada: Delphi consensus on selecting preventable and treatable conditions.* Canadian Medical Association journal = journal, 2011. **183**(12): p. E928-32.

20. Pottie, K., et al., *Evidence-based clinical guidelines for immigrants and refugees.* Canadian Medical Association Journal, 2011. **183**(12): p. E824-E925.

21. Rusińska, A., et al., *Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland—recommendations of the polish Society of Pediatric Endocrinology and Diabetes and the expert panel with participation of national specialist consultants and representatives of scientific societies—2018 update.* Frontiers in Endocrinology, 2018. **9**: p. 246.

22. National Institute for, H. and E. Care, *Vitamin D: supplement use in specific population groups.* NICE, 2014(November 2014): p. 1-54.

23. Alberta Medical Association. *Vitamin D Testing and Supplementation*. 2014 [cited 2022; clinical practice guidelines (CPGs)]. Available from: https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/Vitamin%20D%20Testing%20and%20Supplementation.pdf.

24. Dai, Z., et al., *Methodological quality of public health guideline recommendations on vitamin D and calcium : a systematic review protocol.* BMJ Open, 2019. **9**(11): p. e031840-e031840.

25. Adit A. Ginde, Mark C. Liu, and Carlos A. Camargo Jr, *Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004.* Arch Intern Med, 2009. **169**(6): p. 626–632-626–632.

26. Government of Ontario, *Clinical Utility of Vitamin D Testing An Evidence-Based Analysis Medical Advisory Secretariat Ministry of Health and Long-Term Care How to Obtain Issues in the Ontario Health Technology Assessment Series Conflict of Interest Statement.* Ontario Health Technology Assessment Series Ont Health Technol Assess Ser 2010. **10**(102): p. 1-95.

27. Ministry of Health- British Columbia, *Vitamin D Testing Protocol.* 2010.

28. Pilz, S., et al., *Vitamin D testing and treatment: a narrative review of current evidence.* Endocrine Connections, 2019. **8**(2): p. R27-R43.

29. Hanley, D.A., et al., *Vitamin D in adult health and disease: A review and guideline statement from osteoporosis Canada.* Cmaj, 2010. **182**(12): p. 1-9.

30. Brouwers, M.C., et al., *Development of the AGREE II, part 2: assessment of validity of items and tools to support application.* CMAJ CMAJ • JULY, 2010. **13**(10): p. 182-182.

31. Brouwers, M.C., et al., *APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II*. 2017.

32. Hayawi, L.M., et al., *Screening for osteoporosis: A systematic assessment of the quality and content of clinical practice guidelines, using the AGREE II instrument and the IOM Standards for Trustworthy Guidelines.* PLoS ONE, 2018. **13**(12).

33. Zhou, X., et al., *Quality and Specific Concerns of Clinical Guidelines for Integrated Chinese and Western Medicine: A Critical Appraisal.* Evidence-based Complementary and Alternative Medicine, 2020. **2020**: p. 1-11.

34. Yousef, S., L.M. Hayawi, and G.A. Wells, *A Systematic Assessment of the Quality and the Content of the Immigrant's Health and Vitamin D's Clinical Practice Guidelines (CPGs) using the AGREE II Instrument*, in *PROSPERO #CRD42021240562*. 2021.

35. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. 2022; Available from: https://training.cochrane.org/handbook/PDF/v6.3.

36. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic Reviews, 2015. **4**(1): p. 1-1.

37. Brouwers, M.C., *APPRAISAL OF GUIDELINES fOR RESEARCH & EVALUATION II - AGREE NEXT STEPS CONSORTIUM MEMBERSHIP*. 2009.

38. Armstrong, J.J., et al., *Quality assessment of osteoporosis clinical practice guidelines for physical activity and safe movement: an AGREE II appraisal.* Archives of Osteoporosis, 2016: p. 1-10.

39. Font-Gonzalez, A., et al., *Fertility preservation in children, adolescents, and young adults with cancer: Quality of clinical practice guidelines and variations in recommendations.* Cancer, 2016. **122**(14): p. 2216-2223.

40. Ou, Y., et al., *A Critical Appraisal and Comparison of the Quality and Recommendations of Glaucoma Clinical Practice Guidelines.* Ophthalmology, 2011. **118**: p. 1017-1023.

41. Cicchetti, D.V., *Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology.* Psychological Assessment, 1994(4): p. 284-290.

42. Zimmerman, C., L. Kiss, and M. Hossain, *Migration and Health: A Framework for 21st Century Policy-Making.* PLoS Medicine, 2011. **8**(5): p. 1-7.

43. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis.* Systematic Reviews, 2019. **8**(1): p. 1-6.

44. Holick, M.F., et al., *Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline.* The Journal of Clinical Endocrinology & Metabolism, 2011. **96**(7): p. 1911-1930.

45. Benson, J. and S. Skull, *Hiding from the sun - vitamin D deficiency in refugees.* Aust Fam Physician. , 2007. **36**(5): p. 355-7.

46. Moher, D., L. Stewart, and P. Shekelle, *Implementing PRISMA-P: recommendations for prospective authors.* Systematic Reviews, 2016. **5**(1): p. 15-15.

4.2 Assessment of the quality and content of clinical practice guidelines for vitamin D and for immigrants using the AGREE II instrument: A systematic review

Section overview

Section 4.2 is a manuscript for the systematic review. The AGREE II instrument was used to evaluate CPGs consistent with the IOM definition and relevant to vitD and immigrants' health. Moreover, the content of the identified guidelines was evaluated to clarify whether recommendations for immigrant populations were included in vitD guidelines, and whether vitD recommendations were included in immigrants' health guidelines.

Although vitD deficiency among immigrants was globally detected more than five decades ago, the available CPGs for either vitD or for immigrants' health did not sufficiently address this growing problem at local and international levels. These guidelines were country-specific, not all identified as CPGs, and few met the guideline development criteria.

Manuscript status

This manuscript has been submitted for publication

Said Yousef*; Lamia Hayawi; Alomgir Hossain; Nazmun Nahar; Douglas Manuel; Ian Colman; Manny Papadimitropoulos; MoezAlIslam Faris; Leenah Abdelrazeq; George A Wells

Author roles and contributions

YS, HL, HA, MD, CI, PM, and WG conceived the study. YS designed and executed the search strategy. YS and HL screened and selected the studies for inclusion and performed the data

extraction, synthesis, and analysis. NN and AL retrieved the full-text studies and verified the extracted data. YS drafted the manuscript, which was reviewed by MD, HL, FM, and AL. All authors have approved the version of the manuscript submitted for publication.

Assessment of the quality and content of clinical practice guidelines for vitamin D and for immigrants using the AGREE II instrument: A systematic review

Said Yousef*; Lamia Hayawi; Alomgir Hossain; Nazmun Nahar; Douglas Manuel; Ian Colman; Manny Papadimitropoulos; MoezAlIslam Faris; Leenah Abdelrazeq; George A Wells

*Corresponding author

Said Yousef, MSc*
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Lamia Hayawi, MD, MSc.
Children's Hospital of Eastern Ontario Research Institute,
Ottawa, ON, Canada
lhayawi@cheo.on.ca

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

Nazmun Nahar,
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
nnahar@ottawaheart.ca

Douglas Manuel, MD, MSc.
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,

600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

Leenah Abdelrazeq,
Carlton University, Faculty of Health Sciences, Ottawa, Canada, K1S 5B6
leenahabdelrazeq@cmail.carleton.ca

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Worldwide, more immigrants experience vitamin D (vitD) deficiency than non-immigrants. Recommendations in current clinical practice guidelines (CPGs) concerning vitD are inadequate to address vitD deficiency among immigrants, and there are concerns regarding the quality of guidance in these CPGs. This study identified and evaluated the quality of published CPGs addressing vitD and immigrants' health using the AGREE II tool, and clarified the recommendations pertaining to vitD and immigrant populations in these CPGs. We performed a systematic search for the most recent CPGs across various electronic databases (Ovid MEDLINE® ALL, EMBASE, and Turning Research Into Practice), guideline repositories, and grey literature. Two reviewers independently conducted study selection and data abstraction, and evaluated the quality of the included guidelines using the AGREE II tool. We identified 21 relevant CPGs; 19 focused on vitD and two covering immigrants' health. Around one-quarter of the included CPGs were high quality (≥60% in at least four of the six domains, including "rigor of development"). The highest mean scores among the six AGREE II domains were for "scope and purpose" and "clarity of presentation." One of the 19 CPGs on vitD (5.3%) included immigrants in the final recommendations. VitD recommendations were either emphasized or mentioned as a limitation in the two immigrants' health CPGs. CPGs covering immigrants' health and vitD were inadequately systematically appraised in terms of quality. Moreover, recommendations regarding vitD were insufficient to address the growing epidemic of vitD deficiency among immigrant populations. National and international CPGs that properly address vitD deficiency among immigrants are needed to bridge the gaps between research, policy, and practice. These guidelines should support

vitD screening and supplementation for specific vulnerable immigrant population groups (e.g., different ethnicities/origins) and consider culturally appropriate interventions.

PROSPERO registration number: CRD42021240562

Keywords: Vitamin D, Serum 25-hydroxyvitamin D (S-25(OH)D), Clinical practice guideline, Immigrants; AGREE II

Introduction

Immigrants are a fundamental part of the Canadian population and policy framework [1]. Nearly 22% of the Canadian population are first-generation immigrants [2], meaning immigrants' health impacts Canada's overall healthcare system. Health deterioration among immigrants is a global concern [3-6]; their physical and mental health often declines quickly following arrival in their host countries [4, 7-9], and further health changes occur over 5–10 years [4, 10, 11]. Mechanisms underlying this health decline in immigrants have not been explicitly identified [4, 7], but previous studies suggested it may be explained by changes in psychosocial factors and lifestyles after immigration [7, 8, 12-14].

Globally, immigrants have lower Serum 25-hydroxyvitamin D (S-25(OH)D) levels compared with native-born populations [2, 15, 16]. It was recently suggested that lower levels of serum vitD may partly explain immigrants' health deterioration over time [17]. An analysis of national Canadian data for immigrants from 153 countries and more than 13 ethnicities reported ethnicity was strongly associated with serum vitD status [2]. Non-Western immigrants were also identified by the European Calcified Tissue Society as a specific group at higher risk for vitD deficiency that should receive vitD supplementation [18]. Moreover, vitD status varies among immigrants based on skin pigmentation, clothing type, place/region of birth, and resettlement changes in diet, physical activity, and sun exposure [15, 19, 20].

Clinical practice guidelines (CPGs) are based on scientific evidence and provide up-to-date knowledge, speed the translation of research into practice, improve the effectiveness and quality of care, and decrease variations in healthcare practices [21-23]. The Institute of Medicine (IOM)

defined CPGs as “statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options” [21]. Currently, CPGs pertaining to vitD vary among countries and organizations in terms of their scope, targeted populations, and recommendations [24-27]. In recent decades, recommendations and general guidance have become widely available to manage and accommodate health-related issues among immigrants [11, 28, 29]. These publications focused on screening, infectious diseases, mental health, chronic diseases, treatment, and immunization [11, 28, 29]. Notably, some available publications met the criteria for definition as CPGs [11] that were inadequately systematically appraised in terms of quality [28]. Moreover, current recommendations for vitD were considered inadequate to address the growing epidemic of vitD deficiency in immigrant populations [26, 30], and no attention was given to certain ethnic groups that may be at higher risk for vitD deficiency [24, 26, 31-33]. The 2011 Canadian Immigrant and Refugee Guideline referred to the first 5 years following immigration to Canada as the time during which the “healthy immigrant effect” begins to decline. However, the authors noted that their guideline did not highlight vitD deficiency among immigrants as an emerging condition [11].

Concerns have also been raised about the overall quality of available CPGs [28, 34, 35]. Therefore, to address these concerns in relation to guidelines on vitD and immigrants’ health, we used the validated Appraisal of Guidelines for Research and Evaluation-II (AGREE II) instrument. AGREE II is widely used to assess guideline quality and define information that needs to be reported, and is considered a useful tool to inform guideline development [36, 37]. AGREE II assessment covers the quality of the guideline and whether or not the guideline would be recommended for use [37].

However, previous studies that assessed the quality of CPGs using the AGREE II instrument were inconsistent in how they determined high-quality. For example, with inclusion of the "rigor of development" domain, a high-quality score was reported as ≥60% in at least three of the six domains [28], four of the six domains [38], or in all six domains [39]. Therefore, to overcome gaps in knowledge concerning vitD and immigrants' health, we systematically evaluated CPGs that were consistent with the IOM definition and were relevant to vitD and immigrants' health using the AGREE II instrument. Moreover, we evaluated the content of identified guidelines to clarify whether recommendations for immigrant populations were included in vitD guidelines, and whether vitD recommendations were included in immigrants' health guidelines.

Methods

Study design and research questions

The protocol for this systematic review was registered with PROSPERO (CRD42021240562) [40] and publication [41]. We followed the Cochrane methodology [42] to identify and select CPGs, and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide the reporting [43]. A systematic critical appraisal of available CPGs was performed to critically evaluate the quality of CPGs relevant to either immigrants' health or vitD. We also sought to answer two research questions: 1) "Do CPGs for immigrants' health include recommendations on vitD?" and 2) "Do CPGs for vitD include recommendations for immigrants?

Search strategy and selection of CPGs

A systematic literature search was performed to identify CPGs on vitD and immigrants\refugees worldwide. The primary search was completed in Ovid MEDLINE(R) ALL. The final search

strategy was then translated to EMBASE Classic + Embase (Ovid), as well as the Turning Research Into Practice (TRIP) database. To identify relevant grey literature, we searched well-known guideline developers, such as the Guidelines International Network, Joanna Briggs Institute, World Health Organization (WHO), Healthcare Research and Quality, and National Institute for Health and Care Excellence (NICE). Supplemental searches were performed using backward chaining (looking through the bibliographies in identified guidelines for additional relevant guidelines). The Canadian Agency for Drugs and Technologies in Health filter for searching keywords in guidelines was used [44, 45]. The search was restricted to guidelines published between 2010 and 2020 and studies involving humans. The full search strategy was developed with the help of a medical librarian at Berkman Library, University of Ottawa Heart Institute. The Ovid MEDLINE search strategy is available in Supplementary File 1.

Eligibility criteria

We included guidelines that conformed to the IOM definition of CPGs [21] and concerned immigrants' health or vitD. The full-text guidelines included in our analysis must have been published in the English language between 2010 and 2020, with recommendations intended for healthcare professionals on screening, diagnosis, management, or treatment related to immigrants' health or vitD. Any CPG concerning vitD that emphasized care for people at risk for vitD deficiency in terms of evaluation, treatment, and prevention was also evaluated, without age and sex restrictions. CPGs that included immigrants as a primary population were evaluated without age and sex restrictions. The immigrant population (including refugees and asylum seekers) was defined as those who moved cross-country or were international migrants residing in a destination country, irrespective of legal status and generation [46, 47].

Exclusion criteria

We excluded CPGs that focused on certain chronic diseases, were non-English language, were incomplete text guidelines, and those that did not consider immigrants or vitD as the primary objective. We also excluded guidelines that were not intended for healthcare practice or focused on unhealthy populations (e.g., patients with osteoporosis or vitD deficiency). Evaluating evidence in nutritional guidelines was beyond the scope of this review. Furthermore, we excluded position and consensus papers as well as any other documents that were not equivalent to CPGs.

Outcomes

The primary outcome of this review was the quality score of the included CPGs based on the AGREE II tool. The secondary outcomes were recommendations relating to vitD as part of immigrant guidelines and recommendations in vitD guidelines that targeted immigrant populations.

Selection of CPGs and data extraction

We used the "Covidence" (www.covidence.org) systematic review software to remove duplicates, screen the titles and abstracts, and screen the full-text of identified CPGs. The AGREE II instrument (https://www.agreetrust.org) was used to evaluate the quality of the included guidelines. This tool comprises 23 items and evaluates six domains: "scope and purpose," "stakeholder involvement," "rigor of development," "clarity of presentation," "applicability," and "editorial independence" [37]. Using an online electronic standardized form, two reviewers (YS and HL) independently evaluated and rated each CPG using a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree) [37]. The items scoring sheet of AGREE II tool is presented

in (Supplementary File 2). Furthermore, the reviewers evaluated the content of each CPG and any additional supporting documents that were cited in the published guidelines. Any disagreements regarding assessment were resolved by discussion with a third reviewer to reach consensus. Two reviewers (YS and HL) extracted the main characteristics of the included CPGs, and the extracted data were checked by two reviewers (NN or AL).

Quality evaluation and data synthesis

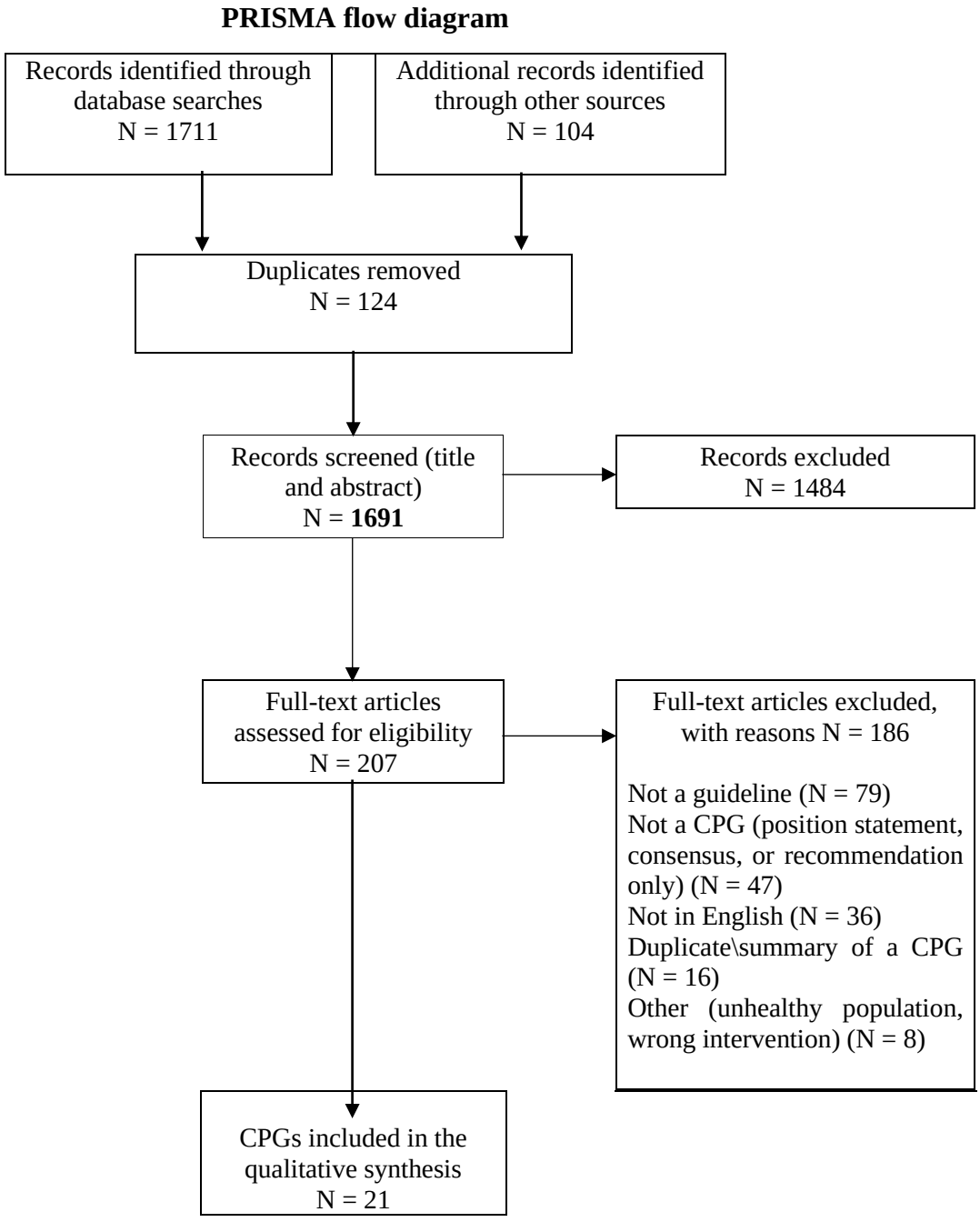
The reviewers' decisions on the overall quality of recommendations contained in the guidelines were based on the context in which the AGREE II was being used. We used the mean scores for each AGREE II domain to calculate total domain scores by summing scores for individual items in a domain. The total domain score was then scaled as a percentage of the maximum possible score for that domain. The formula used to standardize the domain scores was: ([actual score − minimum score] / [maximum score − minimum score]) × 100%. The range of each standardized domain score was 0%–100% [48]. The maximum possible score was obtained by multiplying the maximum score for each domain (strongly agree) by the number of items in the domain and the number of reviewers. Similarly, the minimum possible score was obtained by multiplying the minimum score for each domain (strongly disagree) by the number of items in the domain and the number of reviewers [48]. CPGs were considered high quality when the score was ≥60% in at least four of the six domains, including the "rigor of development" domain [38, 49-51]. Agreement between the two reviewers was assessed for the 23 items using two-way, random, single unit, absolute agreement intra-class correlation coefficients (ICC) [52]. Based on previous research, we classified an ICC of <0.40 as poor or fair, 0.40–0.60 as moderate, 0.61–0.80 as good, and 0.81–

1.00 as excellent [49]. The availability of recommendations for vitD in immigrant guidelines and the inclusion of "immigrant populations" in vitD guidelines were reported descriptively.

Results

The PRISMA flow diagram (Figure 1) shows the systematic process we followed to include studies captured by the electronic search. In total, 1815 citations were returned by our search. After removing duplicates and screening titles and abstracts, 207 articles were identified for full-text review. We excluded 186 articles after the full-text review because they were not a guideline, not a CPG (i.e., position statement, consensus, or recommendation only), not in English, duplicate records, summary of a CPG, or other reasons (e.g., unhealthy population or wrong intervention).

Fig. 1. Literature search and inclusion flowchart (PRISMA model).



We identified 21 records as CPGs; 19 that addressed vitD [24, 25, 31-33, 53-66] and two that covered immigrants' health [11, 67]. Eight CPGs were from Europe [24, 25, 33, 53, 55, 56, 58, 64], seven were from North America [11, 31, 32, 54, 57, 59, 61], three were from Australia [62, 66, 67], and two were from Asia [63, 65], one was from South America [60]. The majority of CPGs (18/21; 85.7%) were developed by official organizations such as academic institutions, governments, health associations, or guideline development organizations [11, 24, 25, 31-33, 54, 55, 57-64, 66, 67]. The remaining three guidelines were developed by non-official organizations [53, 56, 65]. Four of the included CPGs were described as updates of previously published guidelines [24, 59, 64, 66].

Of the 19 CPGs focused on vitD, only one guideline [62] considered immigrants in the recommendations. That guideline emphasized the importance of vitD screening for newly arrived refugees. One of the two immigrants' health CPGs [67] recommended checking "vitamin D status as part of the initial health assessment if there are one or more risk factors for low vitamin D." Moreover, that guideline recommended "treating people with low vitamin D to restore their levels to the normal range with either daily dosing or high dose therapy, ensuring adequate calcium intake, paired with advice about sun exposure and self-management." The second immigrants' health CPG emphasized that vitD deficiency was an emerging condition that was not recognized by the expert panel that developed the guideline [11] (Table 1).

Table 1. Characteristics of the included CPGs.

ID	Author, year	Title	Organization (country/region)	CPG scope	Recommendation for immigrants in vitD CPGs	Recommendation on vitD in immigrants' health CPGs
1	Marcinowska-Suchowierska, 2010 [53]	Vitamin D supplementation in adults—guideline	Poland	VitD supplementation in adults	No recommendations	NA
2	Holick, 2011 [54]	Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline	Endocrine Society, US	Evaluation, treatment, and prevention of vitD deficiency	No recommendations	NA
3	Pottie, 2011 [11]	Evidence-based clinical guidelines for immigrants and refugees	Canadian Collaboration for Immigrant and Refugee Health, Canada	Clinical preventive recommendations for immigrants and refugees	NA	No recommendations The topic of vitD deficiency was unrecognized and reported by the panel as a limitation of this CPG
4	WHO, 2012 [55]	Vitamin D supplementation in pregnant women	WHO, Geneva, Switzerland	VitD supplementation during pregnancy	No recommendations	NA
5	Pludowski, 2013 [56]	Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe	Central Europe	VitD intake in the general population and groups at risk for vitD deficiency	No recommendations	NA
6	Moyer, 2013 [57]	Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force Recommendation Statement	U.S. Preventive Services Task Force (USPSTF), US	VitD and calcium supplementation to prevent fractures in adults	No recommendations	NA
7	National Osteoporosis Society, 2013) [58]	Vitamin D and bone health: A practical clinical guideline for patient management	National Osteoporosis Society (NOS), UK	Management of vitD deficiency in adults (patients or at risk for developing bone disease)	No recommendations	NA
8	Alberta Medical Association, 2014 [59]	Vitamin D testing and supplementation	Alberta Medical Association	VitD testing and supplementation	No recommendations	NA

ID	Author, year	Title	Organization (country/region)	CPG scope	Recommendation for immigrants in vitD CPGs	Recommendation on vitD in immigrants' health CPGs
9	Maeda, 2014 [60]	Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D	Brazilian Society of Endocrinology and Metabology (SBEM), Brazil	Diagnosis and treatment of hypovitaminosis D	No recommendations	NA
10	NICE, 2014 [25]	Vitamin D: supplement use in specific population groups	NICE, UK	Prevent vitD deficiency among specific population groups	No recommendations	NA
11	LeFevre, 2015 [61]	Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force Recommendation Statement	U.S. Preventive Services Task Force (USPSTF), US	Screening for vitD deficiency in adults	No recommendations	NA
12	South Australian Health Perinatal Practice Guideline, 2016 [62]	Vitamin D status in pregnancy	South Australia Maternal, Neonatal & Gynaecology Community of Practice, Australia	VitD management for women and their newborns	VitD screening for "newly arrived refugees"	NA
13	Chaves, 2016 [67]	Recommendations for comprehensive post-arrival health assessment for people from refugee-like backgrounds.	Australasian Society for Infectious Diseases and Refugee Health Network of Australia, Australia	Health assessment for newly arrived people (refugees)	NA	Recommendations: • Check vitD status (assessment for any risk factor for low vitD) • Treat people with low vitD levels and ensuring adequate calcium intake with advice about sun exposure and self-management
14	Khadilkar, 2017 [63]	Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics	Indian Academy of Pediatrics (IAP), India	Prevention and treatment of deficiency of vitD and calcium in the Indian context	No recommendations	NA
15	Royal Osteoporosis Society, 2018 [64]	Vitamin D and bone health: A practical clinical guideline for patient management	The Royal Osteoporosis Society (ROS), UK	VitD patient management	No recommendations	NA

ID	Author, year	Title	Organization (country/region)	CPG scope	Recommendation for immigrants in vitD CPGs	Recommendation on vitD in immigrants' health CPGs
16	Haq, 2018 [65]	Clinical practice guidelines for vitamin D in the United Arab Emirates	United Arab Emirates	Overcome the high incidence of vitD deficiency and to improve overall health	No recommendations	NA
17	South Australian Paediatric Clinical Practice Guidelines, 2018 [66]	South Australian paediatric clinical practice guidelines vitamin D deficiency in children	South Australia Child & Adolescent Health Community of Practice, Australia	Assessment (including investigations) and management of vitD deficiency	No recommendations	NA
18	USPSTF, 2018 [31]	Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults	U.S. Preventive Services Task Force (USPSTF), US	VitD supplementation, with or without calcium, to prevent fractures	No recommendations	NA
19	Rusinska, 2018 [24]	Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland—Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel with Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 update	Polish Society of Pediatric Endocrinology and Diabetes, Poland	Prevention, diagnosis, and treatment of vitD deficiency	No recommendations	NA
20	British Columbia Guidelines, 2019 [32]	Vitamin D testing	Medical Services Commission, British Columbia, Canada	VitD testing in the general population in British Columbia	No recommendations	NA
21	WHO, 2020 [33]	WHO antenatal care recommendations for a positive pregnancy experience Nutritional interventions update: Vitamin D supplements during pregnancy	WHO, Geneva, Switzerland	VitD supplements during pregnancy	No recommendations	NA

CPG, clinical practice guideline; NICE, National Institute of Health and Care Excellence; VitD, vitamin D; WHO, World Health Organization; NA, not applicable.

More than one-quarter of the included CPGs (28.6%) were scored as high quality (≥60% in at least four of the six domains, including “rigor of development”) [11, 25, 31, 33, 54, 55]. The three highest total AGREE II domain scores were for the two CPGs developed by the WHO [33, 55] and the CPG developed by NICE [25] (Table 2).

Table 2. AGREE II total score (%) for each domain in each guideline (N = 21).

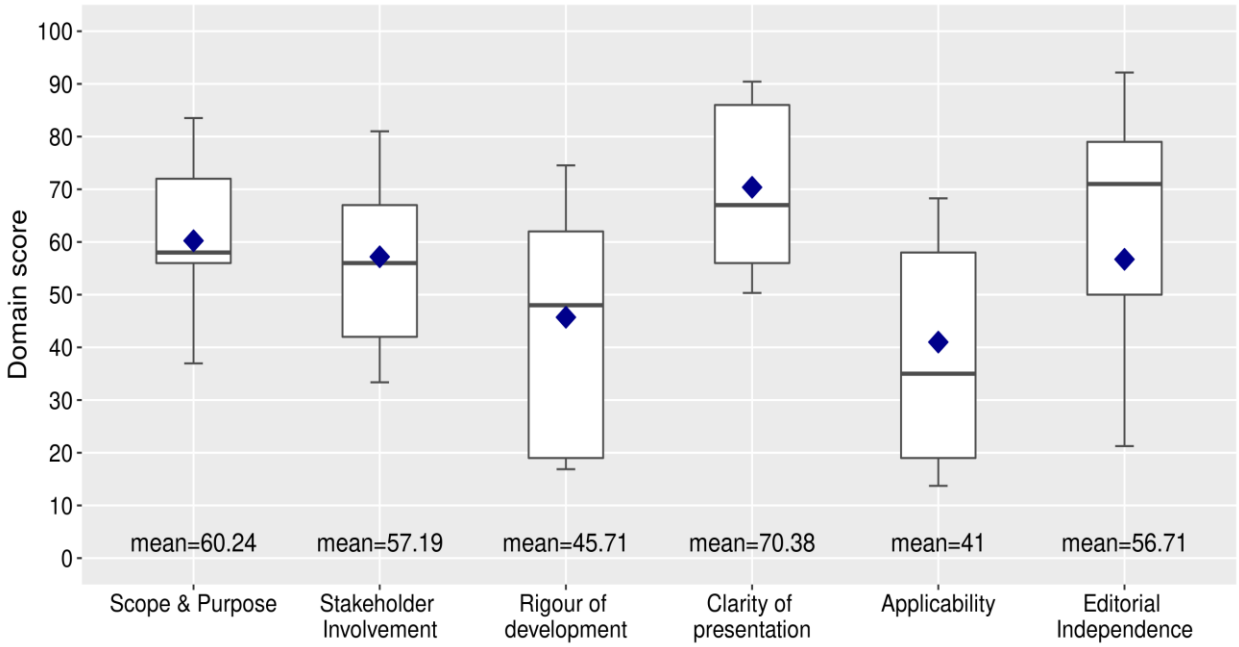
ID	Author, year	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence
1	Marcinowska-Suchowierska, 2010 [53]	0	3	0	28	0	0
2	Holick, 2011 [54]	56	58	73	83	52	79
3	Pottie, 2011 [11]	72	86	79	92	88	100
4	WHO, 2012 [55]	100	89	100	100	75	100
5	Pludowski, 2013 [56]	42	56	8	53	4	0
6	Moyer, 2013 [57]	81	58	50	67	35	71
7	National Osteoporosis Society, 2013 [58]	56	42	44	64	25	50
8	Alberta Medical Association, 2014 [59]	67	67	40	83	33	79
9	Maeda, 2014 [60]	58	44	52	83	31	50
10	NICE, 2014 [25]	92	92	75	94	90	71
11	LeFevre, 2015 [61]	56	50	52	50	33	75
12	South Australian Health Perinatal Practice Guideline, 2016 [62]	64	39	10	56	15	0
13	Chaves, 2016 [67]	72	94	48	86	62	79
14	Khadilkar, 2017 [63]	58	53	19	50	12	71
15	Royal Osteoporosis Society, 2018 [64]	36	25	31	75	19	58
16	Haq, 2018 [65]	47	33	17	61	40	0
17	South Australian Paediatric Clinical Practice Guidelines, 2018 [66]	22	36	6	39	10	0
18	USPSTF, 2018 [31]	67	67	62	64	50	83
19	Rusinska, 2018 [24]	58	56	56	89	48	79
20	British Columbia Guidelines, 2019 [32]	67	67	44	64	58	50
21	WHO, 2020 [33]	94	86	94	97	81	96

NICE, National Institute of Health and Care Excellence; WHO, World Health Organization.

The overall ICC consistency between the AGREE II appraisers was good, with a mean (range) of 63% (47%–90%). Supplementary File 3 presents the ICC results.

The mean (standard deviation [SD]) scores for the six AGREE II domains were 60.2% (23.3%) for scope and purpose, 57.2% (23.8%) for stakeholder involvement, 45.7% (28.8%) for rigor of development, 70.4% (20.1%) for clarity of presentation, 41.0% (27.3%) for applicability, and 56.7% (35.5%) for editorial independence (Figure 2).

Fig. 2. Overall AGREE II scores for each domain.



Blue diamond: mean; horizontal line: median; Error bars: standard deviation.

Discussion

Although vitD deficiency among immigrants is a global issue that was detected more than five decades ago [11, 15, 16, 28, 68, 69], available vitD CPGs were country-specific and varied in their recommendations. Moreover, few of these publications met the criteria for guideline development, as not all were defined as CPGs, and only one considered the immigrant population in the recommendations. The two immigrants' health guidelines were defined as CPGs, and the rigor of development domain scores of these two CPGs were good compared with CPGs on vitD. One of the two CPGs focused on immigrants' health covered vitD testing and treatment, whereas the topic of vitD deficiency was highlighted as a limitation in the other CPG.

Our analysis showed that CPGs for vitD and those for immigrants' health tended to be relatively poor in terms of acknowledging the growing vitD deficiency among vulnerable immigrant populations both in general, and in specific populations (e.g., refugees and certain ethnicities/origins). A recent publication focused on Canadian immigrants found ethnicity was strongly associated with S-25(OH)D levels (2), with the highest deficiency levels among immigrants who were born in Morocco (55.9%), India (34.4%), and Lebanon (about 30%) compared with native-born Canadians (7.45%). Moreover, compared with the white ethnic grouping, the Japanese had the highest level of vitD deficiency, followed by Arabs and Southeast Asians [2]. In our protocol for this systematic review [41], we planned to categorize available information based on immigration status (general immigrants, refugees, and asylum seekers), ethnicity, region/country of birth, host country, and other factors (e.g., type of interventions) depending on their availability in the included guidelines. However, we were unable to specify or categorize information by immigrant subgroups, country, or intervention type because of the

limited information regarding vitD; that is, relevant recommendations in only one immigrants' health CPG [67] and one vitD CPG [62].

Based on AGREE II scores, nearly one-quarter of the included CPGs were evaluated as high-quality. The quality of CPGs was associated with the developer (e.g., well-known international organizations), with the three highest quality CPGs being those from the WHO (2012) [55], NICE (2014) [25], and WHO (2020) [33]. The quality of the included CPGs was not associated with the publication year (result not shown), which was consistent with previous systematic reviews [38, 70], but contrasted with others [28, 39, 49]. Consistent with previous studies [28, 38, 71], the mean scores for the "clarity of presentation" and "scope and purpose" domains in our study were better than those for the other domains. We believe that including "rigor of development" as an important domain for quality assessment offered a more meaningful quality evaluation method. The mean quality score for the rigor of development domain in this study was low (45.7%), although there were large variations in this domain among the included CPGs (e.g., SD 28.8%). The highest domain scores were for the two WHO CPGs (2012 and 2020) [33, 55].

In addition to the incorrect identification of some guidelines as CPGs and the low-quality of available CPGs that were not fully being used in practice, our study highlighted an urgent need for both national and international CPGs that address the growing problem of vitD deficiency among immigrants. In addition, a previous study highlighted the need for a global guideline that specifies sub-immigrant populations for which the evidence and recommendations may differ from the overall immigrant population [72]. Therefore, it is necessary to develop CPGs based on the latest available evidence. CPGs bridge the gaps between research, policy, and practice and support vitD screening and supplementation for vulnerable immigrant populations, including those from certain

ethnicities/origins or groups at particular risk. It is also important that such guidelines also reflect culturally appropriate interventions that consider people of different religious faiths.

Strengths and limitations

The present systematic review focused on guidelines that were defined as CPGs and intended to improve the effectiveness and quality of care and decrease variations in healthcare practices among the targeted populations based on scientific evidence. This study reduced the knowledge gap by exploring an area that has not been investigated in previous systematic reviews pertaining to this topic. As translating CPGs from other languages was a concern in this study, we included CPGs that were published in English and excluded those for which the full-text was found in other languages, which might have introduced selection bias. The included CPGs were restricted to a 10-year period (2010–2020) to capture the most recent or updated CPGs that most likely used rigorous guideline development criteria, which also might have introduced selection bias. However, this method was used to select a set of CPGs as examples for the recently published CPGs in order to assess their quality and content.

Guidance on updating CPGs was unclear and inconsistent, with some authors suggesting that an update is generally required after 3–5 years, whereas a recent systematic review of methodological handbooks for updating CPGs suggested 2–3 years was the most frequently reported time for an update [71].

Conclusion

We found the identified CPGs for immigrants' health and vitD were inadequately systematically appraised in terms of quality. Moreover, currently available recommendations for vitD were

insufficient to address the growing epidemic of vitD deficiency among immigrant populations. Therefore, we support previous recommendations regarding the need for national and international CPGs that respond to the growing problem of vitD deficiency among immigrants. Gathering evidence regarding vitD screening and supplementation for specific vulnerable immigrant population groups (e.g., those from different ethnicities or origins) will support development of CPGs that can bridge the gaps between research, policy, and practice. It is also important that such guidelines recommend culturally appropriate interventions that consider different religious faiths.

Authors' contributions: YS, HL, HA, MD, CI, PM, and WG conceived the study. YS designed and executed the search strategy. YS and HL screened and selected the studies for inclusion and performed the data extraction, synthesis, and analysis. NN and AL retrieved the full-text studies and verified the extracted data. YS drafted the manuscript, which was reviewed by MD, HL, FM, and AL. All authors have approved the version of the manuscript submitted for publication.

Funding: This research did not receive any specific grant from any funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors have declared that no competing interests exist.

Acknowledgement: We thank Sarah Visintini, MLIS (Berkman Library, University of Ottawa Heart Institute), and Becky Skidmore, MLIS, Ottawa, ON, for peer review the MEDLINE search strategy.

Supporting material

Supplementary File 1. Ovid MEDLINE search strategy. Ovid MEDLINE(R) ALL 1946 to October 14, 2020. Date Run: October 15, 2020

1	exp Vitamin D/
2	vitamin D.tw.
3	exp vitamin d deficiency/
4	((avitaminosis or hypovitaminosis) adj1 (D or D2 or D3)).tw,kf.
5	or/1-4
6	exp "Emigrants and Immigrants"/
7	"Emigration and Immigration"/
8	"Transients and Migrants"/
9	refugees/
10	asylum seeker/
11	(alien? or emigrat* or emigrant? or foreigner? or immigrat* or immigrant? or migrant? or migrate? or migration? or migrating or undocumented worker? or foreign born or refugee? or asylum seeker?).tw.
12	or/6-11
13	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
14	(guideline* or standards or consensus* or recommendat*).ti.
15	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
16	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
17	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
18	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
19	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
20	or/13-19
21	(5 or 12) and 20

22	exp animals/
23	exp animal experimentation/ or exp animal experiment/
24	exp models animal/
25	nonhuman/
26	exp vertebrate/ or exp vertebrates/
27	exp humans/
28	exp human experimentation/ or exp human experiment/
29	or/22-26
30	or/27-28
31	29 not 30
32	21 not 31
33	limit 32 to yr="2010 - 2020"
34	(conference abstract or conference review).pt.
35	33 ot 34

Supplementary File 2. AGREE II Checklist, items scoring sheet.

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7** Strongly Agree
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.							
	2. The health question(s) covered by the guideline is (are) specifically described.							
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.							
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.							
	5. The views and preferences of the target population (patients, public, etc.) have been sought.							
	6. The target users of the guideline are clearly defined.							
Rigor of development	7. Systematic methods were used to search for evidence.							
	8. The criteria for selecting the evidence are clearly described.							
	9. The strengths and limitations of the body of evidence are clearly described.							
	10. The methods for formulating the recommendations are clearly described.							
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.							
	12. There is an explicit link between the recommendations and the supporting evidence.							
	13. The guideline has been externally reviewed by experts prior to its publication.							
	14. A procedure for updating the guideline is provided.							
Clarity of presentation	15. The recommendations are specific and unambiguous.							
	16. The different options for management of the condition or health issue are clearly presented.							
	17. Key recommendations are easily identifiable.							
Applicability	18. The guideline describes facilitators and barriers to its application.							
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.							
	20. The potential resource implications of applying the recommendations have been considered.							
	21. The guideline presents monitoring and/ or auditing criteria.							
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.							

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	**2**	**3**	**4**	**5**	**6**	**7** Strongly Agree
	23. Competing interests of guideline development group members have been recorded and addressed.							
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**1** *Lowest possible quality*	**2**	**3**	**4**	**5**	**6**	**7** *Highest possible quality*
Overall Guideline Assessment	2. I would recommend this guideline for use.	*Yes*		*Yes, with modifications*				*No*

Supplementary File 3.

Table S3. Intraclass Correlation Coefficients (between the two raters).

Author, year	ICC (95% CI)
Marcinowska-Suchowierska, 2010 [53]	0.74 (0.48, 0.88)
Holick, 2011 [54]	0.79 (0.56, 0.91)
Pottie, 2011 [11]	0.68 (0.38, 0.85)
WHO, 2012 [55]	0.63 (0.32, 0.83)
Pludowski, 2013 [56]	0.73 (0.46, 0.88)
Moyer, 2013 [57]	0.48 (−0.09, 0.79)
National Osteoporosis Society, 2013 [58]	0.78 (0.55, 0.90)
Alberta Medical Association, 2014 [59]	0.90 (0.78, 0.96)
Maeda, 2014 [60]	0.54 (0.19, 0.77)
NICE, 2014 [25]	0.50 (0.14, 0.75)
LeFevre, 2015 [61]	0.65 (0.10, 0.87)
South Australian Health Perinatal Practice Guideline, 2016 [62]	0.70 (0.41, 0.86)
Chaves, 2016 [67]	0.62 (0.29, 0.82)
Khadilkar, 2017 [63]	0.73 (0.46, 0.87)
Royal Osteoporosis Society, 2018 [64]	0.66 (0.35, 0.84)
Haq, 2018 [65]	0.51 (0.04, 0.77)
South Australian Paediatric Clinical Practice Guidelines, 2018 [66]	0.47 (0.10, 0.73)
USPSTF, 2018 [31]	0.64 (0.03, 0.86)
Rusinska, 2018 [24]	0.52 (0.15, 0.76)
British Columbia Guidelines, 2019 [32]	0.48 (−0.04, 0.78)
WHO, 2020 [33]	0.50 (0.11, 0.75)

CI, confidence interval; ICC, intraclass correlation coefficient; NICE, National Institute of Health and Care Excellence; WHO, World Health Organization.

Supplementary File 4. PRISMA checklist

Section and topic	Item	Checklist item	Yes/No
TITLE			
Title	1	Identify the report as a systematic review.	Yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Yes
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Yes
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Yes
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Yes
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Yes
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Yes
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Yes
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Yes
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Yes

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Yes
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Yes
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Yes
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Yes
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Yes
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Yes
Study characteristics	17	Cite each included study and present its characteristics.	Yes
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Yes
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Yes
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Yes

DISCUSSION	23a	Provide a general interpretation of the results in the context of other evidence.	Yes
Discussion	23b	Discuss any limitations of the evidence included in the review.	Yes
	23c	Discuss any limitations of the review processes used.	Yes
	23d	Discuss implications of the results for practice, policy, and future research.	Yes
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Yes
Competing interests	26	Declare any competing interests of review authors.	Yes
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Yes

NA; not applicable

References

1. Gushulak, B.D. and L.S. Williams, *National Immigration Health Policy Existing Policy, Changing Needs, and Future Directions.* CANADIAN JOURNAL OF PUBLIC HEALTH, 2004. **95**(3): p. 1-27.
2. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.
3. Fernando, G.D.M. and K. Eagan, *The deterioration of health status among immigrants to Canada.: EBSCOhost*, in *Vol. 5, No. 5, September 2010, 462478*. 2010. p. 462-478.
4. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
5. Sanou, D., et al., *Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review.* Journal of Immigrant and Minority Health, 2014. **16**(1): p. 24-34.
6. Vang, Z., et al., *The Healthy Immigrant Effect in Canada: A Systematic Review.* Population Change and Lifecourse Strategic Knowledge Cluster Discussion Paper Series/Un Réseau stratégique de connaissances Changements de population et parcours de vie Document de travail 2015. **3**(1): p. 4.
7. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.
8. Kennedy, S., J.T. McDonald, and N. Biddle, *The Healthy Immigrant Effect and Immigrant Selection: Evidence from Four Countries.* 2006.
9. Hansson, E., et al., *Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement*, in *for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada*. 2010.
10. Newbold, B., *Health status and health care of immigrants in Canada: a longitudinal analysis.* Journal of Health Services Research & Policy Nursing & Allied Health Database 2005. **10**(2).
11. Pottie, K., et al., *Evidence-based clinical guidelines for immigrants and refugees.* CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 2011. **183**: p. E824-925.
12. Chiu, M., et al., *Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-ethnic Study.* Canadian Journal of Cardiology, 2012. **28**(1): p. 20-26.
13. Beiser, M., *The International refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada*. 1993.

14. Williams, D.R., et al., *Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities.* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 69-101.

15. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.

16. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

17. Yousef, S., et al., *Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data.* Nutrients, 2022. **14**(9): p. 1760.

18. Lips, P., et al., *Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society.* European journal of endocrinology, 2019. **180**(4): p. P23-P54.

19. Centers for Disease Control Prevention. *Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination.* . 2013; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf.

20. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

21. Graham, R., et al., *Clinical Practice Guidelines We Can Trust*. Clinical Practice Guidelines We Can Trust. 2011.

22. Kredo, T., et al., *Guide to clinical practice guidelines: the current state of play.* International Journal for Quality in Health Care, 2016. **28**(1): p. 122-122.

23. Shiffman, R.N., et al., *Bridging the guideline implementation gap: a systematic, document-centered approach to guideline implementation.* Journal of the American Medical Informatics Association, 2004. **11**(5): p. 418-426.

24. Rusinska, A., et al., *Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies-2018 Update.* Frontiers in endocrinology, 2018. **9**: p. 246.

25. NICE, *Vitamin D: supplement use in specific population groups.* NICE, 2014: p. 1-55.

26. Alberta Medical Association, *Toward Optimized Practice (TOP) Working Group for Vitamin D. Guideline for Vitamin D Testing and Supplementation in Adults. Edmonton, AB: Toward Optimized Practice.* 2012.

27. Dai, Z., et al., *Methodological quality of public health guideline recommendations on vitamin D and calcium : a systematic review protocol.* BMJ Open, 2019. **9**(11): p. e031840-e031840.

28. Agbata, E.N., et al., *Migrant Healthcare Guidelines: A Systematic Quality Assessment.* Journal of Immigrant and Minority Health, 2019. **21**(2): p. 401-413.

29. Swinkels H, P.K., Tugwell P, Rashid M, Narasiah L, *Development of guidelines for recently arrived immigrants and refugees to Canada: Delphi consensus on selecting preventable and treatable conditions.* Canadian Medical Association journal = journal, 2011. **183**(12): p. E928-32.

30. Adit A. Ginde, Mark C. Liu, and Carlos A. Camargo Jr, *Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004.* Arch Intern Med, 2009. **169**(6): p. 626–632-626–632.

31. USPSTF, *Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Preventive Medication.* U.S. Preventive Services Task Force, 2018.

32. British Columbia Guidelines, *Vitamin D Testing.* Clinical Practice Guidelines and Protocols in British Columbia, 2019.

33. WHO, *Nutritional interventions update: vitamin D supplements during pregnancy.* World Health Organisation Guidelines, 2020.

34. Pilz, S., et al., *Vitamin D testing and treatment: a narrative review of current evidence.* Endocrine Connections, 2019. **8**(2): p. R27-R43.

35. Hanley, D.A., et al., *Vitamin D in adult health and disease: A review and guideline statement from osteoporosis Canada.* Cmaj, 2010. **182**(12): p. 1-9.

36. Brouwers, M.C., et al., *Development of the AGREE II, part 2: assessment of validity of items and tools to support application.* CMAJ CMAJ • JULY, 2010. **13**(10): p. 182-182.

37. Brouwers, M.C., et al., *APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II*. 2017.

38. Hayawi, L.M., et al., *Screening for osteoporosis: A systematic assessment of the quality and content of clinical practice guidelines, using the AGREE II instrument and the IOM Standards for Trustworthy Guidelines.* PLoS ONE, 2018. **13**(12).

39. Zhou, X., et al., *Quality and Specific Concerns of Clinical Guidelines for Integrated Chinese and Western Medicine: A Critical Appraisal.* Evidence-based Complementary and Alternative Medicine, 2020. **2020**: p. 1-11.

40. Yousef, S., L.M. Hayawi, and G.A. Wells, *A Systematic Assessment of the Quality and the Content of the Immigrant's Health and Vitamin D's Clinical Practice Guidelines (CPGs) using the AGREE II Instrument*, in *PROSPERO #CRD42021240562*. 2021.

41. Yousef, S., et al., *Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: a protocol for systematic review.* Systematic Reviews, 2022. **11**(1): p. 1-5.

42. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3*. 2022 February 2022 [cited October 2022 8]; Available from: www.training.cochrane.org/handbook.

43. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Annals of internal medicine, 2009. **151**(4): p. 264-269.

44. de Boeck, K., C. Castellani, and J.S. Elborn, *Medical consensus, guidelines, and position papers: A policy for the ECFS.* Journal of Cystic Fibrosis, 2014. **13**(5): p. 495-498.

45. Lunny, C., et al., *Validation of five search filters for retrieval of clinical practice guidelines produced low precision.* Journal of Clinical Epidemiology, 2020. **117**: p. 109-116.

46. WHO, *Report on the health of refugees and migrants in the WHO European region: no public health without refugee and migrant health.* 2018.

47. WHO. *Refugee and migrant health*. 2022 May 2022 [cited 2022 Oct. 2022]; Available from: https://www.who.int/news-room/fact-sheets/detail/refugee-and-migrant-health.

48. Brouwers Melissa C. *APPRAISAL OF GUIDELINES fOR RESEARCH & EVALUATION II -AGREE NEXT STEPS CONSORTIUM MEMBERSHIP*. 2009; Available from: www.agreetrust.org.

49. Armstrong, J.J., et al., *Quality assessment of osteoporosis clinical practice guidelines for physical activity and safe movement: an AGREE II appraisal.* Archives of Osteoporosis, 2016: p. 1-10.

50. Font-Gonzalez, A., et al., *Fertility preservation in children, adolescents, and young adults with cancer: Quality of clinical practice guidelines and variations in recommendations.* Cancer, 2016. **122**(14): p. 2216-2223.

51. Ou, Y., et al., *A Critical Appraisal and Comparison of the Quality and Recommendations of Glaucoma Clinical Practice Guidelines.* Ophthalmology, 2011. **118**: p. 1017-1023.

52. Hallgren, K.A., *Computing inter-rater reliability for observational data: an overview and tutorial.* Tutorials in quantitative methods for psychology, 2012. **8**(1): p. 23.

53. Marcinowska-Suchowierska, E., et al., *Vitamin D supplementation in adults - guidelines.* Endokrynologia Polska, 2010. **61**: p. 723-9.

54. Holick, M.F., et al., *Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline (Journal of Clinical Endocrinology and Metabolism (2011) 96, (1911-1930)).* Journal of Clinical Endocrinology and Metabolism, 2011. **96**: p. 3908.

55. WHO, *Guideline: Vitamin D supplementation in pregnant women*. 2012, Geneva: World Health Organization.

56. Pludowski, P., et al., *Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe - recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency.* Endokrynologia Polska, 2013. **64**: p. 319-27.

57. Moyer, V.A. and U.S.P.S.T. Force, *Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement.* Annals of internal medicine, 2013. **158**: p. 691-6.

58. National Osteoporosis Society. *Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management*. National Osteoporosis Society [Guideline] 2013; 1-28]. Available from: https://strwebprdmedia.blob.core.windows.net/media/ef2ideu2/ros-vitamin-d-and-bone-health-in-adults-february-2020.pdf.

59. Alberta Medical Association. *Vitamin D Testing and Supplementation*. 2014 [cited 2022; clinical practice guidelines (CPGs)]. Available from: https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/Vitamin%20D%20Testing%20and%20Supplementation.pdf.

60. Maeda, S.S., et al., *Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D.* Arquivos brasileiros de endocrinologia e metabologia, 2014. **58**: p. 411-33.

61. LeFevre, M.L. and U.S.P.S.T. Force, *Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement.* Annals of internal medicine, 2015. **162**: p. 133-40.

62. S.A. Health Perinatal Practice Guideline, *Vitamin D status in pregnancy.* SA Health Perinatal Practice Guidelines, 2016.

63. Khadilkar, A., et al., *Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics (IAP) Guidelines.* Indian pediatrics, 2017. **54**: p. 567-573.

64. Royal Osteoporosis Society. *Vitamin D and Bone Health:A Practical Clinical Guideline for Patient Management*. Royal Osteoporosis Society [Guideline] 2018; 1-25].

65. Haq, A., et al., *Clinical practice guidelines for vitamin D in the United Arab Emirates.* The Journal of steroid biochemistry and molecular biology, 2018. **175**: p. 4-11.

66. S.A. Health Paediatric Clinical Practice Guideline, *Vitamin D Deficiency in Children.* SA Health Paediatric Clinical Practice Guidelines, 2018.

67. Chaves Nj, P.G.B.B.A.T.A.S.M.W.J.G.J.D.J.S., *Recommendations for comprehensive post-arrival health assessment for people from refugee-like backgrounds.* Australasian Society for Infectious Diseases, 2016: p. 1-189.

68. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D*, in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.

69. Cashman, K.D., et al., *Vitamin D deficiency in Europe: pandemic?* The American journal of clinical nutrition, 2016. **103**(4): p. 1033-44.

70. Kung, J., R.R. Miller, and P.A. Mackowiak, *Failure of clinical practice guidelines to meet institute of medicine standards: two more decades of little, if any, progress.* Archives of internal medicine, 2012. **172**(21): p. 1628-1633.

71. Vernooij, R.W., et al., *Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks.* Implementation Science, 2014. **9**(1): p. 1-9.

72. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis.* Systematic Reviews, 2019. **8**(1): p. 1-6.

Chapter 5: Global status of vitamin D among immigrants

Chapter overview

Chapter 5 consists of three sections in which the global vitD status of first-generation immigrants compared with the native-born population of the host country are systematically investigated. The focus was to identify the concentration levels (mean/median) of S-25(OH)D among immigrants and their distribution in different regions and countries. Results pertaining to the concentration levels of S-25(OH)D were planned in the systematic review proposal (Section 5.1) and preliminary results of the systematic review are reported including the determinants specific to immigrants (Section 5.2). These results in terms of their global distribution are also illustrated in maps (Section 5.3).

This chapter addresses the third set of research questions for this thesis: What is the global status of vitD among first-generation immigrants compared with the native-born population of the host country? Do the same immigrants in one host country (e.g., Syrians in Canada) have the same S-25(OH)D levels in another host country (e.g., Syrians in Germany)? What are the key global determinants of deficient or insufficient S-25(OH)D levels among first-generation immigrants?

Chapter contents

Section 5.1 presents the protocol of the systematic review and meta-analysis. This protocol was registered in PROSPERO and published in the *Journal of Systematic Reviews*.

Section 5.2 presents the initial results of the systematic review and meta-analysis related to the global concentration levels of vitD among first-generation immigrants.

Section 5.3 provides sample maps for immigrants by region, host country, and country of birth or origin compared with non-immigrants based on the findings of the main systematic review.

5.1 Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations-a systematic review and meta-analysis

Section overview

This section presents a protocol highlighting the background, search strategy and other methodological aspects, and a brief rationale for a systematic review to compare the levels of vitD between ethnic groups of immigrants in different regions with those of native-born populations and to identify the possible associations between vitD deficiency and disease status among immigrants. This protocol was registered with PROSPERO (CRD42018086729) in 2018 and published in 2019.

Manuscript status

This manuscript has been published: *Systematic Reviews (2019) 8:211. doi.org/10.1186/s13643-019-1123-4*

Said Yousef*, Jesse Elliott, Douglas Manuel, Ian Colman, Manny Papadimitropoulos, Alomgir Hossain, Nathalie Leclair, and George A. Wells.

Author roles and contributions

YS, MD, CI, PM, HA, and GW conceived the study. LN designed and executed the search strategy. YS and JE will screen, select the studies for inclusion, and perform the data extraction. YS drafted the protocol, which was revised by all authors. All authors have approved the version of the manuscript submitted for publication.

Related thesis appendices

Appendix A5:

The PDF of the PROSPERO (CRD42018086729) registration Appendix A5.1.

The PDF of the published protocol is presented in Appendix A5.2.

Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations-a systematic review and meta-analysis

Said Yousef[1,2*], Jesse Elliott[1,2], Douglas Manuel[3,4,5], Ian Colman[1,6], Manny Papadimitropoulos[7,8], Alomgir Hossain[1,4], Nathalie Leclair[9] and George A. Wells[1,2]

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Jesse Elliott
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
jelliott@ottawaheart.ca

Douglas Manuel, MD, MSc
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Alomgir Hossain, Ph.D.

School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

Nathalie Leclair,
Leclair, Berkman Library, University of Ottawa Heart Institute, Ottawa, ON, Canada.
nathalie.leclair@uottawa.ca

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Background: A growing body of literature indicates that, worldwide, immigrants experience health deterioration after their arrival into their adopted country, and moreover, they have lower vitamin D compared to the native-born population. We plan to review if the levels of vitamin D are comparable between different ethnic groups in different regions of the world with those of native-born populations and to identify the possible associations between vitamin D deficiency and disease status among immigrants.

Methods/design: A systematic review and meta-analysis will be conducted following the methods of the Cochrane handbook for systematic reviews. A literature search was performed to identify studies on immigrants and vitamin D. The primary outcome is vitamin D levels, and the secondary outcome is any vitamin D deficiency-related disease. Study design and participant characteristics will be extracted, including ethnicity, country of birth and/or origin, and the host country. Descriptive and meta-analytic summaries of the outcomes will be derived. Distiller-SR and RevMan will be used respectively for data management and meta-analysis.

Discussion: This systematic review may partially help clarify vitamin D-related health deterioration in migrants; moreover, to develop a global guideline that specifies sub-populations, in which the evidence and vitamin D-related recommendations might differ from the overall immigrant population.

Systematic review registration: PROSPERO CRD42018086729

Keywords: Systematic review, Meta-analysis, Vitamin D, Immigrants' health deterioration

Background

Healthy people are more likely to migrate, and those with serious medical conditions may be disqualified [1, 2]. Despite particular groups, such as refugees, who are not as healthy as other immigrants, substantial evidence indicates that the health of immigrants at the time of arrival is significantly better than the health of the native-born population of the host country [3-8]. Recent studies have shown that the physical and mental health of immigrants declines after their arrival into the adopted country [2, 4, 8-12], and health changes can occur within 5 to 10 years [9, 13-15]. Migration studies suggest that the integration process is likely a new experience for immigrants, in which changes in the environment and lifestyle are well-documented factors predisposing migrants to chronic diseases [8, 16, 17]. Moreover, migration experience and post-migration integrations are believed to explain the decline in the health status of immigrants [4, 11, 18]. However, the mechanistic reasons underlying the decline in immigrants' health have not been explicitly identified [4, 14]. Worldwide research evidence suggests that migration is a significant risk factor for low vitamin D levels due to resettlement changes in lifestyle and sun exposure [19-22]. Vitamin D plays a crucial role in physiological functions; it regulates the absorption of calcium and phosphorus that support both skeletal (bone hemostasis) and non-skeletal health [23, 24].

The dietary sources for vitamin D are plant-based foods (e.g., mushroom) which include vitamin D2 (ergocalciferol) and the animal-based foods (e.g., salmon and tuna fish) which include vitamin D3 (cholecalciferol) [21, 25]. In addition to the natural food-based sources, the human body obtains vitamin D from artificial sources such as supplements and fortified food. The primary source, however, is through skin exposure to the sunlight (cutaneous synthesis of vitamin D) [26], and therefore, vitamin D is commonly known as the 'sunshine vitamin' because the body can make it through exposure to sunlight whereas most other vitamins are food-based ingestion [27].

However, the ability of body to create and maintain sufficient levels affected by socio-demographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and the latitude), cultural and religious factors (e.g., clothing, sedentary behaviors and prolonged breastfeeding time), lifestyle and dietary factors (e.g., vegetarian diet), as well as genetic and health factors (e.g., skin pigmentation and obesity) [20, 23, 28-30]. A study on people from different ethnic origin who have similar practices proposes that skin pigmentation is possibly the most significant risk factor for vitamin D deficiency irrespective of the ultraviolet light exposure [31].

The concentration of 25-hydroxyvitamin D serum (25(OH)D) represents the combined contributions of the cutaneous synthesis and the dietary intake of vitamin D and is considered the best clinical indicator for the overall adequacy of vitamin D [23, 25, 27]. There is no international agreement regarding the reference range for serum 25(OH) D concentrations. The Institute of Medicine (IOM) has developed different categories for the concentration levels of the serum 25(OH)D in blood, which include optimal (> 75 nmol/l), sufficient (> 50 nmol/l), inadequate or deficient (≤ 50 nmol\l), and deficient (< 30 nmol/l) levels [27]. According to the World Health Organization, the levels of serum 25(OH)D below 50 nmol/l were classified as insufficient and levels below 25 nmol/l were considered as deficient [32].

Vitamin D deficiency is a global pandemic health problem in all age groups that occurs in countries with both high and low levels of sunlight (degree of the latitudes) [23, 24]. Hilger et al. in a systematic review of studies from 44 countries with data from 112 articles (168,389 participants), reported a wide range of serum 25(OH)D between 4.9 and 136.2 nmol/l with age and sex variations. Mean levels of < 50 nmol/l were reported in one third of these studies [33]. The highest

levels of serum 25(OH)D were among participants who live in North America while those who live in the Middle East and Africa regions have much lower levels [33].

Studies show that worldwide migrant populations, including refugees and asylum, have lower levels of vitamin D compared with the local populations [20, 30, 34]. Refugees are considered at particularly higher risk for vitamin D deficiency due to staying indoors to avoid dangers, cold weather, living in high-rise buildings that limit their outdoor activities and sun exposure, and concerns regarding skin cancer [20]. The age, ethnicity, country of origin, higher latitudes, nutritional barriers, cultural practices, and the length of time after immigration were reported in several studies as being associated with the risk of vitamin D deficiency among immigrants [20] [30, 35]. Migrants are often considered as low-SES individuals, and immigrants of low SES were found to have a higher risk of vitamin D deficiency [36], as well as to develop physical and mental illnesses [16, 30, 35].

Previous studies support the hypothesis that the inadequate or deficient level of vitamin D is associated with increased risk of all-cause mortality and a wide range of physical and mental health diseases, including osteoporosis, type 1 diabetes mellitus, cancer, cardiovascular disease, obesity, schizophrenia and depression, and the metabolic syndrome [17, 23, 33, 35, 37-39].

Although there is disagreement about optimal levels of serum 25(OH)D, evidence suggests that levels < 30 nmol/l are associated with an increased risk of some diseases in which vitamin D deficiency has been found to play a role. Moreover, the thresholds for serum 25(OH)D may vary according to different outcomes and subgroups, and the most advantageous levels begin at 75 nmol/l [40-43].

The most relevant systematic review to this protocol published by Martin et al. 2016 has focused on dark skin immigrants including both first- and second-generation immigrants. Moreover, the included studies were selected from certain regions associated with dark skin, namely, Africa; West, South, Central, and Southeast Asia; the Middle East; the Caribbean, and Central America [20]. Whereas the current systematic review will include only the first-generation immigrants who were defined as foreign-born population and no geographical restrictions will be applied. However, to the best of our knowledge, no study has systematically reviewed the vitamin D deficiency related diseases and immigrant status.

The aims of this systematic review and meta-analysis are the following: first is to compare the levels of vitamin D between ethnic groups of immigrants in different regions with those of native-born populations. Consequently, the findings will be used to establish global maps for vitamin D status of immigrants and non-immigrants, as well as maps for the same ethnic immigrants (at high risk) in different geographical regions of the world. Second is to identify the possible associations between vitamin D deficiency and disease status among immigrants.

Methods/design

The protocol of this review has been registered on PROSPERO (CRD42018086729) [44]. The strategy involves a comprehensive systematic review of the literature and meta-analysis. The procedures will follow the methods outlined in the Cochrane handbook for systematic reviews [45]. This includes guidance in planning the review, searching and selecting studies, collecting data, as well as the risk of bias and prospective meta-analysis. The protocol of this systematic

review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) Statement [46]; the checklist is presented in Additional file 1.

Literature search

A systematic literature search was performed to identify studies on immigrants and vitamin D. The primary search strategy was completed in MEDLINE(R) ALL (Ovid) by a medical information specialist using a combination of subject headings and keywords. The strategy was peer-reviewed by an independent information specialist using the Peer Review of Electronic Search Strategies (PRESS) guidelines [47]. The final search strategy was run on August 16, 2018, and translated to EMBASE Classic + Embase (Ovid) (available in Additional file 2), PubMed, and Web of Science Indexes (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI) on the same day, and to Cochrane (Wiley on INSERT DATE). With regard to the grey literature, Dissertations and Theses Global (ProQuest) was searched as well as international and governmental websites, including the World Health Organization (WHO), the Canadian Institute for Health Information (CIHI), and the National Institute for Health Care Excellence (NICE). Supplemental searches will be performed using backward chaining (looking through the bibliographies of included studies for additional relevant articles).

Eligibility criteria and study selection

Two reviewers independently will follow the population, exposure, comparator, and outcomes (PECO) criteria in evaluating the included studies. The population of interest is immigrants, defined as foreign-born. The exposure is the integration process over time in the new environment after immigration, and the comparator is the non-immigrant (native-born population). The primary outcome is vitamin D levels, and the secondary outcome is any vitamin D deficiency-related

disease (e.g., cardiovascular, diabetes, cancer, osteoporosis, depression, chronic pain, and respiratory infections).

All study designs will be eligible except the following publication types: case reports, case series, systematic or narrative reviews, editorials, and commentaries. Studies will be excluded if they do not define or include migrant status, including populations at higher risk for vitamin D deficiency such as chronic illness, and if the concentration levels of vitamin D are not reported. The publication with the largest sample size will be included if the same population is presented in more than one publication. No studies will be excluded from the search based on the language and the study date.

All studies will be independently screened and evaluated for eligibility by two reviewers, and any disagreement will be discussed and resolved by consensus.

Data extraction and synthesis

The data will be extracted by two independent reviewers. If necessary, discrepancies will be resolved through discussion [46]. Standardized and piloted forms for data extraction will be used to extract the characteristics of the studies and participants, as well as the specific details from each study (e.g., ethnicity, country of birth and/or origin, and the host country). Data for all immigrants and a priori defined subgroups will be extracted. Based on the availability, the mean and/or the median of the concentration levels of vitamin D will be summarized in a tabular format, pooled via meta-analysis, and used to compare immigrants to non-immigrants. Descriptive statistics will be implemented for the baseline features of the included studies. The vitamin D status will be identified based on the IOM categories (optimal, adequate, insufficient, or deficient) [27]. When the concentration level of vitamin D is given as nanograms per milliliter, it will be multiplied

by 2.496 to attain the nanomoles per liter [48]. Participant and study characteristics of the included studies will be used to assess the clinical and methodological heterogeneity, respectively. The heterogeneity between the included studies will be completed through a visual assessment of forest plots and the calculation of the I^2 statistic, which provides a numerical summary of heterogeneity. The following categories of I^2 statistic will be considered: < 25%, 25 to 50%, and 50 to 75%. For $I^2 > 50$, heterogeneity will be explored using subgroup and meta-regression. If the reason for heterogeneity is identified, it will be reported accordingly. If heterogeneity is not resolved, the results will be pooled for I^2 between 50 and 75%, and a caveat regarding the heterogeneity will be provided. For $I^2 > 75\%$, the results will not be pooled. Outcome data will be pooled using a random-effects model. Distiller SR and RevMan will be used to complete data extraction and meta-analyses, respectively.

Subgroup and sensitivity analysis

Depending on the availability and the quality of data (risk of bias), subgroup analysis will be conducted based on age, sex, ethnicity, country of birth and/or origin, geographical location and the latitude of the host country for immigrants, season, the immigration class (family, economic, and refugee classes), and the time since immigration.

Risk of bias and quality evaluation

The quality of the included studies will be assessed using the relevant tools depending on the study design. These tools may include Joanna Briggs, Scottish Intercollegiate Guidelines Network-Publication no.50 (SIGN50), Risk Of Bias In Non-randomized Studies of Exposure (ROBINSE), as well as Cochrane Collaboration's Risk of Bias tool (ROB v. 2.0) [45, 49-51]. Two independent

reviewers will evaluate the quality, and any disagreements between reviewers will be discussed and resolved by consensus.

Discussion

The baseline risk for vitamin D deficiency is higher among migrants especially those who have darker skin, such as Middle Eastern and African populations, and those who migrate from equatorial region to northern latitude [20, 23, 33]. Cultural and lifestyle practices that minimize sun exposure also increase the risk in these subgroups [20]. However, the developed recommendations for vitamin D supplementation provided in the Dietary Reference Intakes (DRIs) still inadequately address the growing epidemic of vitamin D insufficiency in immigrants and refugees [48]. For instance, the DRIs for vitamin D and calcium sets the recommended of daily intake assuming minimal sun exposure for all populations. Moreover, no additional recommendations are given for sub-populations such as immigrants living in high northern latitudes, those with darker skin pigmentation, or those who wear heavy clothing that inhibits sun exposure [52, 53]. In addition, most of the worldwide guidelines on vitamin D and/or immigrants' health does not entirely address these subpopulations in their recommendations [54-58].

Nonetheless, recent reviews recommended future studies to assess relevant data on vitamin D and determinants, including lifestyle factors with a subgroup comparison of the population within the same country [33], as well as further research specific to migrant populations to establish links between immigrant status and disease status [17]. Therefore, this systematic review may partially help to clarify vitamin D-related health deterioration in migrants and moreover, to develop a global guideline that specifies sub-populations, in which the evidence and recommendation might differ from the overall immigrant population.

Supporting material

Additional file 1: Revised PRISMA-P checklist.

Additional file 2: Search strategy.

Abbreviations

25(OH)D: 25-Hydroxyvitamin D serum; A&HCI: Arts and Humanities Citation Index (1975–present); CIHI: Canadian Institute for Health Information; CPCIS: Conference Proceedings Citation Index—Science (1990–present); CPCISSH: Conference Proceedings Citation Index—Social Science and Humanities (1990–present); DRIs: Dietary Reference Intakes; ESCI: Emerging Sources Citation Index (2005–present); IOM: Institute of Medicine; NICE: National Institute for Health Care Excellence; PECO: Population, Exposure, Comparator, and Outcomes; PRESS: Peer Review of Electronic Search Strategies; PRISMAP: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol; ROB: Risk of bias tool; ROBINS-E: Risk Of Bias In Non-randomized Studies of Exposure; SCI-EXPANDED: Science Citation Index Expanded (1900–present); SIGN50: Scottish Intercollegiate Guidelines Network-Publication no. 50; SSCI: Social Sciences Citation Index (1900–present); WHO: World Health Organization.

Acknowledgements

We thank Becky Skidmore, MLS, Ottawa, ON, for the peer review of the MEDLINE search strategy and subsequent translations to the other databases.

Authors' contributions

YS, MD, CI, PM, HA, and GW conceived the study. LN designed and executed the search strategy. YS and JE will screen, select the studies for inclusion, and perform the data extraction. YS drafted the protocol, which was revised by all authors. All authors have approved the version of the manuscript submitted for publication.

Funding

No funding

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable Consent for publication Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada.

[2] Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada.

[3] Ottawa Hospital Research Institute, Ottawa, ON, Canada.

[4] Institute for Clinical Evaluative Sciences, Ottawa and Toronto, ON, Canada.

[5] Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada.

[6] Canadian Institutes of Health Research, Ottawa, ON, Canada.

[7] Eli Lilly Canada Inc, Toronto, ON, Canada.

[8] Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.

[9] Berkman Library, University of Ottawa Heart Institute, Ottawa, ON, Canada.

References

1. Laroche, M., *Health status and health services utilization of Canada's Immigrant and non- immigrant populations.* Canadian Public Policy, 2000. **XXCI**(1): p. 51-73.
2. Solé-Auró, A. and E.M. Crimmins, *Health of Immigrants in European countries.* Int Migr Rev, 2008. **42**(4).
3. Chen, J., R. Wilkins, and E. Ng, *Health Expectancy by Immigrant Status, 1986 and 1991.* Health Reports, 1996. **8**(3): p. 29-38.
4. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.
5. Pe'rez, C.E., *Health status and health behaviour among immigrants [Canadian Community Health Survey - 2002 Annual Report] - ProQuest*, in *Ottawa, ON: Statistics Canada, 112, Catalogue 82-003-SIE*. 2002. p. 89-100.
6. Gee, E., K. Kobayshi, and S. Prus, *Examining the "Healthy Immigrant Effect" in Later Life: Findings from the Canadian Community Health Survey - ProQuest*. 2003.
7. Dunn, J. and I. Dyck, *Social Determinants of Health in Canada's Immigrant Population: Results from the National Population Health Survey.* 1998.
8. Hemminki, K., *Immigrant health, our health.* The European Journal of Public Health, 2014. **24**(suppl 1): p. 92-95.
9. Newbold, B., *Self-rated health within the Canadian immigrant population: risk and the healthy immigrant effect.* Social Science & Medicine, 2005. **60**: p. 1359-1370.
10. Kennedy, S., J.T. McDonald, and N. Biddle, *The Healthy Immigrant Effect and Immigrant Selection: Evidence from Four Countries.* 2006.
11. Williams, D.R., et al., *Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities.* Annals of the New York Academy of Sciences, 2010. **1186**(1): p. 69-101.
12. Hansson, E., et al., *Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement*, in *for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada*. 2010.
13. Newbold, B., *Health status and health care of immigrants in Canada: a longitudinal analysis.* Journal of Health Services Research & Policy Nursing & Allied Health Database 2005. **10**(2).
14. Newbold, B., *The short-term health of Canada's new immigrant arrivals: evidence from LSIC.* Ethnicity & Health, 2009. **14**(3): p. 315-336.
15. Zhao, J., L. Xue, and T. Gilkinson, *Health Status and Social Capital of Recent Immigrants in Canada.* Policy Studies, 2010(March).
16. Public Health Agency of, C., *Immigrant Mental Health.* 2010.

17. Renzaho, A.M.N., J.A. Halliday Bhsci, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review.* Nutrition, 2011. **27**: p. 868-879.

18. Beiser, M., *The International refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada*. 1993.

19. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

20. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.

21. M.H. Edwards, C.N.C.H.C.C., *THE GLOBAL EPIDEMIOLOGY OF VITAMIN D STATUS • JARCP The Journal of Aging Research & Clinical Practice*, in *The Journal of Aging Research and Clinical Practice (JARCP)*. 2014.

22. Holick, M.F., *The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health INTRODUCTION: HISTORICAL PERSPECTIVE.* Public Health Reviews, 2010. **32**(1): p. 267-283.

23. Spedding-Simon, *Vitamin D and Human Health*. 2015 ed. 2015, MDPI • Basel • Beijing • Wuhan: Publisher Shu-Kun Lin.

24. Wacker, M. and M.F. Holick, *Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation.* Nutrients, 2013. **5**: p. 111-148.

25. Pham, T., *Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal.* Thesis-McGill University, 2012.

26. Alshahrani, A.A. and S.C. Alicia Garcia, *Vitamin D Deficiency and Possible Risk Factors Among Middle Eastern University Students in London, Ontario, Canada.* 2014.

27. Statistics Canada, *Vitamin D blood levels of Canadians*. 2015.

28. Palacios, C. and L. Gonzalez, *Is vitamin D deficiency a major global public health problem?* Journal of Steroid Biochemistry and Molecular Biology, 2014. **144**: p. 138-145.

29. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D*, in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.

30. Centers for Disease Control Prevention. *Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination.* . 2013; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf.

31. Knoss, R., L.G. Halsey, and S. Reeves, *Ethnic Dress, Vitamin D Intake, and Calcaneal Bone Health in Young Women in the United Kingdom.* Journal of Clinical Densitometry, 2012. **15**(2): p. 250-254.

32. Rosen, C.J., *clinical practice Vitamin D Insufficiency*, in *N Engl J Med*. 2011. p. 248-54.

33. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British Journal of Nutrition, 2014. **111**: p. 23-45.

34. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

35. Gaksch, M., et al., *Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium.* PLOS ONE, 2017. **12**(2): p. e0170791-e0170791.

36. Aucoin, M., et al., *Vitamin D status of refugees arriving in Canada Findings from the Calgary Refugee Health Program.* 2013. **59**.

37. Dong, J.-Y., et al., *Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies.* Nutrients, 2013. **5**(9): p. 3551-3562.

38. Chu, F., et al., *Serum 25-Hydroxyvitamin D Concentrations and Indicators of Mental Health: An Analysis of the Canadian Health Measures Survey.* Nutrients, 2017. **9**(10): p. 1116-1116.

39. Huotari, A. and K.-H. Herzig, *VITAMIN D AND LIVING IN NORTHERN LATITUDES – AN ENDEMIC RISk AREA FOR VITAMIN D DEFICIENCy.* International Journal of Circumpolar HealthInt J Circumpolar Health, 2008. **67**(3).

40. Heaney, R.P., *Vitamin D in Health and Disease.* Clinical Journal of the American Society of Nephrology, 2008. **3**(5): p. 1535-1541.

41. Robyn, L. and N. Rachel, *What is the optimal level of vitamin D? Separating the evidence from the rhetoric clinical*. 2014.

42. Sohl, E., et al., *Thresholds for Serum 25(OH)D Concentrations With Respect to Different Outcomes.* J Clin Endocrinol Metab, 2015. **100**: p. 2480-2488.

43. Bischoff-Ferrari, H.A., et al., *Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes.* The American journal of clinical nutrition, 2006. **84**(1): p. 18-28.

44. Said Abdelrazeq Yousef, George A. Wells, and Jesse Elliot, *Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis*, in *PROSPERO*. 2018, National Institute of Health Research.

45. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. 2022; Available from: https://training.cochrane.org/handbook/PDF/v6.3.

46. Moher, D., L. Stewart, and P. Shekelle, *Implementing PRISMA-P: recommendations for prospective authors.* Systematic Reviews, 2016. **5**(1): p. 15-15.

47. McGowan, J., et al., *PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement.* Journal of Clinical Epidemiology, 2016. **75**: p. 40-46.

48. Adit A. Ginde, Mark C. Liu, and Carlos A. Camargo Jr, *Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004.* Arch Intern Med, 2009. **169**(6): p. 626–632-626–632.

49. Scottish Intercollegiate Guidelines Network, *Sign 50*, in *Diversity*. 2011. p. 2-105.

50. University of, B., *ROBINS-E | Bristol Medical School: Population Health Sciences | University of Bristol*.

51. Sanderson, S., I.D. Tatt, and J.P.T. Higgins, *Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: A systematic review and annotated bibliography.* International Journal of Epidemiology, 2007. **36**(3): p. 666-676.

52. Government of, C., *Vitamin D and Calcium: Updated Dietary Reference Intakes - Canada.ca*, in *Government of Canada website*. 2012.

53. Institute of Medicine, *Dietary Reference Intakes for Calcium and Vitamin D Health Effects of Vitamin D and Calcium Intake.* 2011.

54. Pottie, K., et al., *Evidence-based clinical guidelines for immigrants and refugees.* Canadian Medical Association Journal, 2011. **183**(12): p. E824-E925.

55. Government of Ontario, *Clinical Utility of Vitamin D Testing An Evidence-Based Analysis Medical Advisory Secretariat Ministry of Health and Long-Term Care How to Obtain Issues in the Ontario Health Technology Assessment Series Conflict of Interest Statement.* Ontario Health Technology Assessment Series Ont Health Technol Assess Ser 2010. **10**(102): p. 1-95.

56. Ministry of Health- British Columbia, *Vitamin D Testing Protocol.* 2010.

57. Alberta Medical Association, *Toward Optimized Practice (TOP) Working Group for Vitamin D. Guideline for Vitamin D Testing and Supplementation in Adults. Edmonton, AB: Toward Optimized Practice.* 2012.

58. Royal Children Hospital. *Vitamin D deficiency*. Sept. 2020; Available from: https://www.rch.org.au/clinicalguide/guideline_index/Vitamin_D_deficiency/.

Supporting material

Additional file 1: Revised PRISMA-P checklist [1].

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

PRISMA-P checklist

Section/topic		Checklist item	Yes	No
Identification	1a	Identify the report as a protocol of a systematic review	Yes	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		No
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Yes	
Authors			Yes	
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No
Support				
Sources	5a	Indicate sources of financial or other support for the review	Yes	
Sponsor	5b	Provide name for the review funder and/or sponsor		No
Role of sponsor/ funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		No
INTRODUCTION			Yes	
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	
METHODS				
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes	
STUDY RECORDS				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	
DATA				
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	Yes	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Yes	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Yes	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)		No

Additional file 2: Medline search strategy. (DOCX 34 kb)

Ovid MEDLINE(R) ALL 1946 to August 15, 2018 & Embase Classic+Embase 1947 to 2018 August 15, 2018. Date Run: August 16, 2018

No.	Searches
1	exp Vitamin D/
2	(vitamin D or vitamin D2 or Vitamin D3 or vitamins D or vitamins D2 or Vitamins D3).tw,kf,rn.
3	("25(OH)" or 25OH or 25OHD or 25OHD?).tw,kf,rn.
4	(25OHvitamin? D or 25OHvitamin? D2 or 25OHvitamin? D3).tw,kf,rn.
5	(cholecalciferol? or colecalciferol? or calciol or vigantol or vigorsan or 1C6V77QF41 or 9VU1KI44GP).tw,kf,rn.
6	(hydroxycholecalciferol? or hydroxycolecalciferol? or hydroxycalciferol or hydroxyvitamin? or hydroxy vitamin? or hydroxycalcidiol or calcifediol or calcidiol or calderol or d?drogyl or dydrogil or delakmin or hidroferol or rayaldee or u 32070 or u32070 or T0WXW8F54E).tw,kf,rn.
7	(alfacalcidol or alfarol or alphacalcidol or einsalpha or etalpha or ox?devit? or unalfa or unalpha or URQ2517572).tw,kf,rn.
8	(dihydroxycholecalciferol? or dihydroxycolecalciferol? or dihydroxyvitamin? or dihydroxy vitamin? or osteo d or ro 21 5816 or ro21 5816 or secalciferol or 0AXX2V8L5Z).tw,kf,rn.
9	(calcitriol or dihydroxy-20-epi-vitamin? or bocatriol or bonky or calcijex or caraben sc or cicarol or citrihexal or decostriol or dn 101 or dn101 or ecatrol or hitrol or kolkatriol or kosteo or lemytriol or mc 1288 or mc1288 or meditrol or osteotriol or poscal or renatriol or rocaltrol or rexamat or ro 21 5535 or rocaltrol or roical or rolsical or silkis or sitriol or soltriol or tariol or tirocal or triocalcit or vectica or FXC9231JVHl).tw,kf,rn.
10	(1,25 OHD or 1,25 OHD? or 1,25OHD or 1,25OHD? or 1a,25OHD or 1a,25OHD? or 1a25 OHD or 1a25 OHD?).tw,kf,rn.
11	(ergocalciferol? or hydroxyergocalciferol or afj d2 or alcovit d2 or aldevit or bentavit or calciferol? or calciferovit or chemovit d or chocola d or condol or d arthrin? or d crivit or d vatine or d vital or d2 vita or davitamon d or davitan or davitin or decaps or dee osterol or dee ron or deeosterol or deeron or dekristol or delta monovit or deltabios or deltalin? or deltamonovit or deltar or deltasterolo or deltavit or deradion or deradione or deratol or dergosten or desyn or desyne or detalup or detamine or deterapion? or devitan or devitil or devitol or di actol or di drol or diactol or dibiovit or didrol or didue vita or diergin? or diferol or difilina or difvitamin d or dilavit or disir or disterin# or divit urto or divitin# or dohyfral d or drisdol or dumovit d or dz idrosol or endo d or ercalciol or ergorone or ergosterid? or ergosterin activatum or ergosterina irradiata or ertron? or feroxyl? or fortedol or fortodyl? or genevis or glicol d2 or idro steral or idrosol d2 or infadin? or infron? or inovitan d or irradiated ergosterol or kalciferol or metadee or min# d2 or mulsiferol or mykostin or mykostine or oldevit or oleovit d2 or oleovitamin d2 or ostelin? or osteodin# or osteovit or osteovitadin? or osteovitin# or ostergil or plivit d

	or radiamon or radiosterin# or radiostol or radsterin? or raquiferol or ro 850 or shock ferol or shockferol or sinervit d2 or steral or steramin? or sterobiol or sterodin or sterodine or sterogyl or sterosol or sterovit or sterovitin# or ucemine d or ultranol or urto calciosterina or urtosterin# or uvesterol d or vi de or vi di or videlta or vidi or vidiman or vidolen or vidue monico or viduemonico or vigoncal or vio d or viosterin? or viosterol or vitadit or vitaminol or vitaplex or vitasan d or vitastabil? d or vitastabil d or vitasterin? or vitasterol or vitavel d or wandervit d2 or VS041H42XC).tw,kf,rn.
12	(antitanil or antitetanin? or atecen or calcamin? or calcinosefaktor or dht intensol or dichistrolum or dichyst?rol or dihydral or dihydrotachysterin? or dihydrotachysterol or dihydro tachysterol or dikystrol or dygratyl or hytakerol or manipal or parterol or tachidon or tachystin? or tachystol or tetilan).tw,kf,rn.
13	exp vitamin d deficiency/
14	((avitaminosis or hypovitaminosis) adj1 (D or D2 or D3)).tw,kf.
15	(rickets or ricketts or rachiti*).tw,kf.
16	Osteomalacia?.tw,kf.
17	((Osteodystroph* or mineral) adj2 bone disorder?).tw,kf.
18	or/1-17
19	exp "Emigrants and Immigrants"/
20	"Emigration and Immigration"/
21	"Transients and Migrants"/
22	refugees/
23	Ethnic Groups/
24	minority groups/
25	Minority Health/
26	((ethnic* or minority) adj3 (group? or people? or person? population? or patient? or community or communities or individual?)).tw,kf.
27	(minority adj3 (health or healthcare or ethnic*)).tw,kf.
28	minorities.tw,kf.
29	ethnic*.ti.
30	(alien? or emigrat* or emigrant? or foreigner? or immigrat* or immigrant? or migrant? or migrate? or migration? or migrating or undocumented worker? or foreign born or refugee? or asylum seeker?).tw,kf.
31	(resettlement? or settlement?).tw,kf.
32	(displaced adj3 (family or families or individual? or person? or people? or population? or man or men or wom#n or child or children)).tw,kf.

33	(nationalities or nationality).tw,kf.
34	or/19-33
35	18 and 34
36	animals/ not humans.sh.
37	35 not 36
38	(comment or editorial or interview or news).pt.
39	37 not 38
40	39 use medall
41	exp vitamin D/
42	(vitamin D or vitamin D2 or Vitamin D3 or vitamins D or vitamins D2 or Vitamins D3).tw,kw,rn.
43	("25(OH)" or 25OH or 25OHD or 25OHD?).tw,kw.
44	(25OHvitamin? D or 25OHvitamin? D2 or 25OHvitamin? D3).tw,kw.
45	(cholecalciferol? or colecalciferol? or calciol or vigantol or vigorsan or 1406-16-2 or 67-97-0).tw,kw,rn.
46	(hydroxycholecalciferol? or hydroxycolecalciferol? or hydroxycalciferol or hydroxyvitamin? or hydroxy vitamin? or hydroxycalcidiol or calcifediol or calcidiol or calderol or d?drogyl or dydrogil or delakmin or hidroferol or rayaldee or u 32070 or u32070 or 19356-17-3).tw,kw,rn.
47	(alfacalcidol or alfarol or alphacalcidol or einsalpha or etalpha or ox?devit? or unalfa or unalpha or 41294-56-8).tw,kw,rn.
48	(dihydroxycholecalciferol? or dihydroxycolecalciferol? or dihydroxyvitamin? or dihydroxy vitamin? or osteo d or ro 21 5816 or ro21 5816 or secalciferol or 40013-87-4 or 55721-11-4).tw,kw,rn.
49	(calcitriol or dihydroxy-20-epi-vitamin? or bocatriol or bonky or calcijex or caraben sc or cicarol or citrihexal or decostriol or dn 101 or dn101 or ecatrol or hitrol or kolkatriol or kosteo or lemytriol or mc 1288 or mc1288 or meditrol or osteotriol or poscal or renatriol or rocaltrol or rexamat or ro 21 5535 or rocaltrol or roical or rolsical or silkis or sitriol or soltriol or tariol or tirocal or triocalcit or vectica or 32222-06-3 or 32511-63-0 or 66772-14-3).tw,kw,rn.
50	(1,25 OHD or 1,25 OHD? or 1,25OHD or 1,25OHD? or 1a,25OHD or 1a,25OHD? or 1a25 OHD or 1a25 OHD?).tw,kw,rn.
51	(ergocalciferol? or hydroxyergocalciferol or afj d2 or alcovit d2 or aldevit or bentavit or calciferol? or calciferovit or chemovit d or chocola d or condol or d arthrin? or d crivit or d vatine or d vital or d2 vita or davitamon d or davitan or davitin or decaps or dee osterol or dee ron or deeosterol or deeron or dekristol or delta monovit or deltabios or deltalin? or deltamonovit or deltar or deltasterolo or deltavit or deradion or deradione or deratol or dergosten or desyn or desyne or detalup or detamine or deterapion? or devitan or devitil or devitol or di actol or di drol or diactol or dibiovit or didrol or didue vita or diergin? or diferol or difilina or difvitamin d or dilavit or disir or disterin# or divit urto or divitin# or dohyfral d or drisdol or dumovit d or dz idrosol or endo d or ercalciol or ergorone or ergosterid? or

	ergosterin activatum or ergosterina irradiata or ertron? or feroxyl? or fortedol or fortodyl? or genevis or glicol d2 or idro steral or idrosol d2 or infadin? or infron? or inovitan d or irradiated ergosterol or kalciferol or metadee or min# d2 or mulsiferol or mykostin or mykostine or oldevit or oleovit d2 or oleovitamin d2 or ostelin? or osteodin# or osteovit or osteovitadin? or osteovitin# or ostergil or plivit d or radiamon or radiosterin# or radiostol or radsterin? or raquiferol or ro 850 or shock ferol or shockferol or sinervit d2 or steral or steramin? or sterobiol or sterodin or sterodine or sterogyl or sterosol or sterovit or sterovitin# or ucemine d or ultranol or urto calciosterina or urtosterin# or uvesterol d or vi de or vi di or videlta or vidi or vidiman or vidolen or vidue monico or viduemonico or vigoncal or vio d or viosterin? or viosterol or vitadit or vitaminol or vitaplex or vitasan d or vitastabil? d or vitastabil d or vitasterin? or vitasterol or vitavel d or wandervit d2 or 50-14-6 or 50809-47-7 or 8042-78-2).tw,kw,rn.
52	(antitanil or antitetanin? or at 10 or at10 or atecen or calcamin? or calcinosefaktor or dht intensol or dichistrolum or dichyst?rol or dihydral or dihydrotachysterin? or dihydrotachysterol or dihydro tachysterol or dikystrol or dygratyl or hytakerol or manipal or parterol or tachidon or tachystin? or tachystol or tetilan or 67-96-9).tw,kw,rn.
53	vitamin D deficiency/
54	exp rickets/
55	osteomalacia/
56	((avitaminosis or hypovitaminosis) adj1 (D or D2 or D3)).tw,kw.
57	(rickets or ricketts or rachiti*).tw,kw.
58	Osteomalacia?.tw,kw.
59	((Osteodystroph* or mineral) adj2 bone disorder?).tw,kw.
60	or/41-59
61	exp migrant/
62	exp migration/
63	ethnic group/
64	ancestry group/
65	minority group/
66	minority health/
67	((ethnic* or minority) adj3 (group? or people? or person? population? or patient? or community or communities or individual?)).tw,kw.
68	(minority adj3 (health or healthcare or ethnic*)).tw,kw.
69	minorities.tw,kw.
70	ethnic*.ti.

71	(alien? or emigrat* or emigrant? or foreigner? or immigrat* or immigrant? or migrant? or migrate? or migration? or migrating or undocumented worker? or foreign born or refugee? or asylum seeker?).tw,kw.
72	(resettlement? or settlement?).tw,kw.
73	(displaced adj3 (family or families or individual? or person? or people? or population? or man or men or wom#n or child or children)).tw,kw.
74	(nationalities or nationality).tw,kw.
75	or/61-74
76	60 and 75
77	exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
78	exp human/ or exp human experimentation/ or exp human experiment/
79	77 not 78
80	76 not 79
81	editorial.pt.
82	80 not 81
83	82 use emczd
84	40 or 83
85	remove duplicates from 84

References (additional files)

1. Moher, D., L. Stewart, and P. Shekelle, *Implementing PRISMA-P: recommendations for prospective authors.* Systematic Reviews, 2016. **5**(1): p. 15-15.

5.2 Worldwide vitamin D status of immigrants to non-immigrants: A systematic review and meta-analysis

Section overview

This section presents the initial findings of the systematic review and meta-analysis to compare the levels of vitD between ethnic groups of immigrants in different regions with those of native-born populations and to identify the global determinants for vitD deficiency among immigrants. This work in progress since the literature search needs to be updated and at that time the risk of bias (ROB) and meta-analysis will be completed.

Manuscript status

This manuscript is in preparation.

Said Yousef*, Lamia Hayawi; Maleka Ben Mahdi; Alomgir Hossain; Douglas Manuel; Manny Papadimitropoulos; Ian Colman; MoezAlIslam Faris; George A Wells

Author roles and contributions

YS, MD, CI, PM, HA, and GW conceived the study. LN designed and executed the search strategy. YS, HL screened and selected the included studies. YS and MBM performed the data extraction. YS and HL working on the analysis and preparing the results for the manuscripts. YS drafting the current manuscript.

Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations-a systematic review and meta-analysis

Said Yousef*; Lamia Hayawi; Maleka Ben Mahdi; Manny Papadimitropoulos; Ian Colman; Alomgir Hossain; Douglas Manuel; MoezAlIslam Faris; George A Wells Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Lamia Hayawi, MD, MSc.
Children's Hospital of Eastern Ontario Research Institute,
Ottawa, ON, Canada
lhayawi@cheo.on.ca

Maleka Ben Mahdi
The Gray Clinic, Fraser Health
22722 Lougheed Hwy, Maple Ridge, BC V2x 2v6
M.mahdi@zu.edu.ly

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

Douglas Manuel, MD, MSc
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

Abstract

Objectives: Globally, immigrants have lower Serum 25-Hydroxyvitamin D (S-25(OH)D) levels compared with native-born populations. S-25(OH)D levels also vary among migrants from different ethnic backgrounds and geographic regions. We compared S-25(OH)D levels among first-generation immigrants from different global regions and native-born populations of host countries. We identified the global determinants for vitD deficiency/insufficiency among immigrants. The results were presented in tabular format based on the regions/countries of the host and immigrant populations.

Method: This systematic literature review used five databases, including Medline and EMBASE. Two reviewers independently extracted data from identified literature. We used Distiller-SR for data screening and extraction, RevMan to conduct the meta-analyses.

Results: We identified 35 studies conducted in three regions and 13 countries involving 23,654 individuals (11,113 first-generation immigrants). The majority (n=25) of the included studies were single-arm studies. Migration to the 13 host countries was from over 165 origins and ethnicities. The overall estimated means of S-25(OH)D among immigrants was (44.31) compared to non-immigrants (64.27 nmol/L).

Conclusion: First-generation immigrants have lower S-25(OH)D than non-immigrants. This study offers novel findings pertaining global S-25(OH)D among first-generation immigrants. Developing an international immigrant guideline to integrate and implement strategies for vitD improvement may be warranted.

Introduction

Vitamin D comprises several fat-soluble secosteroids, prohormones, and metabolites [1] and plays a crucial role in physiological functions, including regulating calcium and phosphorus absorption and supporting skeletal (bone hemostasis) and non-skeletal health [1-3]. The concentration of S-25(OH)D represents the combined contributions of dietary intake and cutaneous synthesis of vitD, and is considered the best clinical indicator for the overall adequacy of vitD [2, 4-6]. An insufficient status for vitD of <50 nmol/L has been frequently used to describe hypovitaminosis D, whereas other levels remain controversial. The Institute of Medicine (IOM) recommended maintaining S-25(OH)D concentration levels above 50 nmol/L, whereas other experts favored a concentration of 50–100 nmol/L [7-11]. Moreover, other researchers have indicated that S-25(OH)D thresholds may vary according to different outcomes and subgroups and suggested the most advantageous levels begin at 75 nmol/L [12-15]**.**

Despite the ability of the body to create and maintain sufficient levels of S-25(OH)D, several factors may explain lower levels of S-25(OH)D (<50 nmol/L) among immigrants. These may fall under sociodemographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and latitude), cultural, behavioral, and religious factors (e.g., clothing, sedentary lifestyles, smoking, and prolonged breastfeeding time), lifestyle and dietary factors (e.g., vegetarian diet), and genetic and health-related factors (e.g., skin pigmentation and obesity) [2, 7, 16-20]. A global review of evidence on vitD status and determinants of hypovitaminosis D found the leading risk factors for vitD deficiency were older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, poor dietary

habits, and absence of vitD fortification [7]. Moreover, a more recent systematic review reported skin pigmentation was the most common factor affecting vitD status [19].

Over the past few years, vitD has become an active clinical and epidemiological research topic. Despite the levels of sunlight, vitD deficiency has become a global health problem observed all age groups and regions [2, 21, 22]. Worldwide, an estimated 1 billion people have deficient or insufficient vitD (i.e., S-25(OH)D <50 nmol/L) [23]. Consequently, in the past few decades, scientists have gathered overwhelming evidence linking vitD deficiency to skeletal and non-skeletal health [23, 24]. In a systematic review of studies from 44 countries that included data from 112 articles, a range of S-25(OH)D (4.9–136.2 nmol/l) across the studies was identified, and more than one-third of the studies reported mean levels <50 nmol/L [25]. Migration poses a significant risk factor for low S-25(OH)D levels [19, 21, 26], and vitD deficiency/insufficiency (S-25(OH)D <50 nmol/L) is common among immigrants, especially among refugees [27].

Although there is broad agreement on the fundamental role of vitD in bone health, there remains some controversy concerning its role in non-skeletal health, as well as the threshold and required concentration of S-25(OH)D to achieve health benefits or cause health consequences [2, 8].

The population of first-generation immigrants is unique to this systematic review as previous studies included aggregated generations. Understanding the patterns and distribution of S-25(OH)D levels in different regions and between different groups of first-generation immigrants will inform local and international strategies to reduce vitD deficiency/insufficiency and prevent health-related consequences among first-generation immigrants. Therefore, we designed a systematic review and meta-analysis to investigate the growing global problem of vitD deficiency/insufficiency among first-generation immigrants (foreign-born) compared with non-

immigrants (native-born), and between immigrant groups by ethnicity, region, and country of birth. Moreover, we clarified the global determinants of vitD deficiency/insufficiency among first-generation immigrants. Consequently, the findings will be used to establish global maps for vitamin D status of immigrants and non-immigrants.

This study was designed to answer the following research questions. What is the global status of vitD among first-generation immigrants compared with the native-born population of the host country? Do the same immigrants in one host country (e.g., Syrians in Canada) have the same S-25(OH)D levels in another host country (e.g., Syrians in Germany)? What are the key global determinants of deficient or insufficient S-25(OH)D levels among first-generation immigrants?

Method

Study design and population

The protocol for this systematic review was registered with PROSPERO (CRD42018086729) [29] and then published [30]. We followed the Cochrane methodology [31] to identify and select citations and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide the reporting [32]. We used Distiller-SR for data screening and extraction and RevMan to conduct the meta-analyses.

The study's population, exposure, comparator, and outcomes (PECO) were defined, with the population of interest restricted to first-generation immigrants (defined as foreign-born), including refugees and asylum seekers. The exposure was the integration process over time in the host

country after immigration (immigrants studied inside the host country). The comparator was defined as the native-born population of the host country (non-immigrants). The primary outcome was restricted to the blood concentration levels of S-25(OH)D, which were given as mean or median values. Single-arm studies that included immigrants only were considered part of the population of interest.

Search strategy

A systematic literature search was performed to identify studies on immigrants and vitD. Five databases were searched after the primary search strategy was completed in MEDLINE(R) ALL (Ovid) by a medical information specialist using a combination of subject headings and keywords. The search strategy was peer-reviewed by an independent information specialist using the Peer Review of Electronic Search Strategies (PRESS) guidelines [34]. The final search strategy was run on August 16, 2018, translated to the EMBASE Classic + Embase (Ovid), PubMed, and Web of Science Indexes (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI) on the same day, and then to the Cochrane Library (Wiley on August 17,2018). With regard to relevant grey literature, we searched Dissertations and Theses Global (ProQuest) in addition to international and governmental websites, including the WHO, the Canadian Institute for Health Information (CIHI), and the National Institute for Health and Care Excellence (NICE). The search was updated in March 2020, and second search update is now required. A supplemental search will be performed using backward chaining (looking through the bibliographies of included studies for additional relevant articles). The MEDLINE(R) ALL (Ovid) search strategy was published with the study protocol [29] (Appendix 1).

Eligibility criteria

Two reviewers independently followed the PECO criteria in evaluating the selected studies, which included studies focused on first-generation immigrants or foreign-born populations. We included studies that had mixed generations of immigrants if first-generation immigrants comprised more than 80% of the total immigrant population. Studies that compared immigrants with non-immigrants and studies that only involved immigrants (single arm) were included.

We also included studies in which the levels of S-25(OH)D were given as mean or median values only. Studies that presented vitD status as deficient, insufficient, or used a cut-off point for S-25(OH)D were excluded. Baseline levels of S-25(OH)D were extracted when studies followed participants and had assessments at more than one time point. Levels were included when participants were healthy or at least 80% of the sample was healthy. Studies with large sample sizes were included if the same population was presented in more than one publication.

Studies were excluded if less than 80% of the immigrant population were first-generation immigrants. Studies that included unhealthy people were also excluded. For example, those focused on populations at higher risk for vitD deficiency such as people with osteoporosis. No studies were excluded based on the language or date of publication, but we excluded studies that were case reports, case series, systematic or narrative reviews, editorials, and commentaries.

Outcome

The outcome was S-25(OH)D (mean or median value). The level of S-25(OH)D was expressed in nanograms per milliliter (ng/mL) or nanomoles per liter (nmol/L), in which 1 ng/mL equaled 2.496 nmol/L [10, 23, 35]. We converted S-25(OH)D levels in ng/mL to nmol/L by multiplying the given

values by 2.496 [35]. When the median S-25(OH)D level was given, we used the "bc.mean.sd" function to convert median to mean. This function applies the Box-Cox (BC) method to estimate the sample mean and standard deviation from a study that presented one of the following sets of summary statistics (S). S1: median, minimum and maximum values, and sample size; S2: median, first and third quartiles, and sample size; or S3: median, minimum and maximum values, first and third quartiles, and sample size [36, 37]. Thus, the related-results for the concentration levels of S-25(OH)D may diverge from the initially reported data.

In the protocol for this systematic review, the secondary outcome was planned to be any vitD deficiency-related disease (e.g., cardiovascular, diabetes, cancer, osteoporosis, depression, chronic pain, and respiratory infections). This was changed because our inclusion criteria specified that studies must only include healthy participants (or at least 80% of the sample must be healthy). Therefore, any vitD study that was conducted among patients was excluded. This deviation from the protocol was considered part of the study limitations.

Data selection and extraction

We used the "Distiller" systematic review software to remove duplicates, screen the titles and abstracts, record the study selection, and extract data from the included studies. Two reviewers (YS and HL) independently screened the titles and abstracts of the identified studies based on the eligibility criteria and selected the relevant studies for full-text review. A data extraction sheet was developed based on piloting data extraction from some of the selected studies. In addition to sociodemographic data, the focus was on mean or median values for S-25(OH)D, ethnicity,

country of birth and origin, the host country, length of time after immigration, and vitD determinants (e.g., season, clothing, and skin pigmentation).

Discrepancies or disagreements regarding either screening or selection of studies for full-text review were resolved by discussion to reach consensus [32]. As described in the protocol, the characteristics of the included studies will be used to assess the methodological heterogeneity. The heterogeneity across the included studies will be evaluated using a visual assessment of forest plots and the calculation of I^2 statistics to obtain a numerical summary of heterogeneity.

Quality evaluation and data synthesis

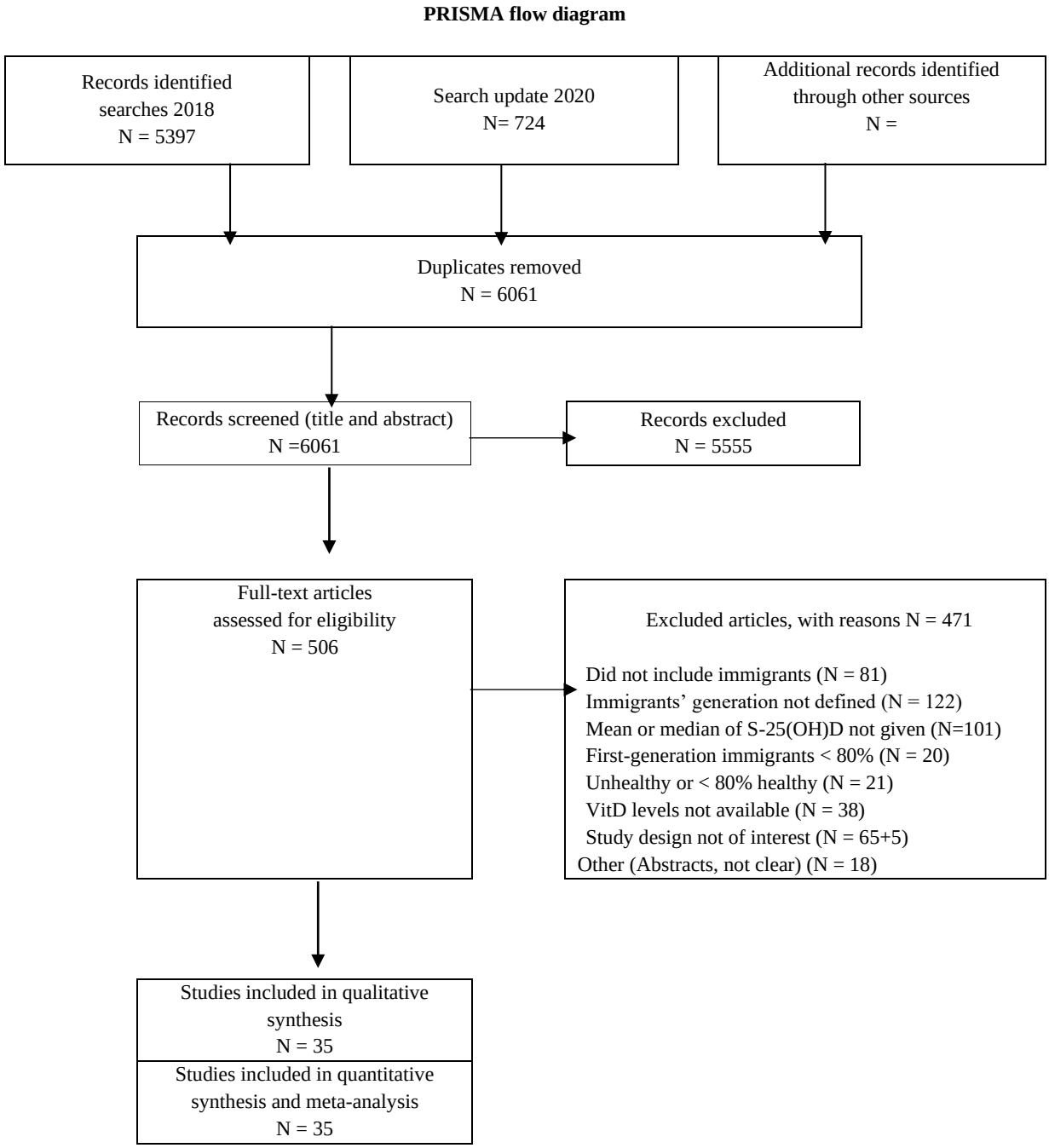
Risk of bias (RoB) will be assessed by two reviewers. As the baseline data were collected from all types of studies, including clinical trials, the National Institutes of Health (NIH) RoB tool will be used [38]. The NIH tool was designed to assess the quality of observational cohort and cross-sectional studies. In addition to overall quality, the NIH RoB tool has 14 appraisal criteria that are assigned ratings of "yes," "no," or "other" (Appendix 2).

As indicated in our protocol [30] and depending on the availability and the quality of data, we planned to carry out subgroup and sensitivity analysis. The following were a priori assigned subgroup analyses: age, sex, ethnicity, country of birth and/or origin, geographical location and the latitude of the host country for immigrants, season, the immigration class (family, economic, and refugee classes), and the time since immigration.

Results

The PRISMA flow diagram (Fig. 1) shows the systematic process we followed to include studies captured by our electronic search. After removing duplicates, 6061 citations were returned in both the 2018 and updated 2020 search. After removing duplicates and screening titles and abstracts, 5555 studies were excluded, which left 506 articles for full-text review. An additional 471 articles were excluded after full-text review because they did not meet the inclusion criteria. Of the 40 full-text articles that were found in languages other than English, only two studies (from Spain and Norway) were eligible and included. Finally, thirty-five studies were included in the qualitative and quantitative synthesis.

Fig. 1. Literature search and inclusion flowchart (PRISMA model).



The table of characteristics (Table 1) presents specific details from the selected studies, including: authors, study design, total sample size, non-immigrants (host country, sample size, age, and sex), immigrants (country of birth or origin, sample size, age, and sex), percentage of first-generation immigrants and immigration status (e.g., refugees), total S-25(OH)D for non-immigrant groups, and vitD for immigrant groups.

The 35 included studies were from three continents and 13 host countries: North America (Canada: n=5; US: n=4). Europe (Norway: n=7; Sweden: n=3; one study each from Switzerland, UK, Belgium, Denmark, Finland, Greece, Netherlands, and Spain), and Australia (n=8). Migration to the 13 host countries was from over 165 origins and ethnicities.

Ten of the included studies were comparison studies and 25 were single-arm studies. Of the 23,654 individuals included in the studies, 11,113 were first-generation immigrants. Twenty-three studies were conducted with participants who were identified first-generation immigrants. In 12 studies immigrant generation was not clearly mentioned, but we assumed that more than 80% of participants were first-generation immigrants based on other information such as length of stay and mean age. Five studies included refugees only and three studies identified participants as both refugees and immigrants, whereas the remaining studies included immigrants that might have been in various immigration classes such as refugees and asylum seekers.

Five studies measured S-25(OH)D using ng/mL, which was converted to nmol/L. Seven studies presented the median S-25(OH)D levels, and medians were converted to means for six studies. In one study [39], we used the median assuming the data were normally distributed. The overall

estimated means of S-25(OH)D among immigrants was (44.31) compared to non-immigrants (64.27 nmol/L).

Other variations in terms of age, sex, immigrants' origins and length of stay in the host countries, assay methodology used to measure S-25(OH)D, seasonal variations, and publication date and type were also compared between the included studies. The initial results presented in this section (5.2) are based on these thirty-five included studies only. The search will be updated, after which we will update the results.

Table 1. Characteristics of the included studies (N=35), with mean S-25(OH)D (nmol/L)

Authors	***Study design***	***N Comparison/ single arm***	***N Host origin (sex, age years)***	***N Immigrants' origin (sex, age years)***	***% 1st generation/ immigration class***	***S-25(OH)D Non-immigrants***	***S-25(OH)D Immigrants***
Stephens et al., 1982 [40]	Cohort study	203 Comparison	44 UK (female & male, adults)	159 South Asian (Pakistani, Indian, Bangladesh) & East Africa (female & male, adults)	100% Immigrants	52.20	20.30
Brunvand et al., 1993 [41]	Cross-sectional	53 Comparison	23 Norway (females, mean 26 ± 4.2)	30 Pakistan (females, mean 28 ± 5.8)	> 80% Immigrants	43.10	15.10
GLERUP et al., 2000 [42]	Cross-sectional	104 Comparison	44 Denmark (females, mean (SEM) 36.1 (1.6))	60 Arab (females, mean (SEM) 32.2 (1.4))	> 80% Immigrants	47.10	7.1
SKULL et al., 2003 [43]	Cross-sectional survey	116 Single arm	Australia	116 Africa (females & males, mean 34)	92% Immigrants	NA	23.60
Meyer et al., 2004 [44]	Cross-sectional	1046 Comparison	869 Norway (men & women, median 60)	177 Pakistan (men & women, median 40)	100% Immigrants	74.80	25.00
Brock et al., 2004 [45]	Cross-sectional	60 Single arm	Australia	60 Chinese (women, elderly)	100% Immigrants	NA	36.00
Holvik et al., 2005 [46]	Cross-sectional	1000 Single arm	Norway	1000 Turkey, Sri Lanka, Iran, Pakistan, Vietnam (men & women)	100% Immigrants	NA	30.00*
Nicolaidou et al., 2006 [47]	Cross-sectional	393 Comparison	344 Greek (females & males, mean 4.8 ± 0.67)	49 Immigrants (females & males, mean 4.8 ± 0.67)	100% Immigrants	83.61	69.58 $
Holvik et al., 2007 [48]	Cross-sectional	721 Comparison	560 Norway (men & women, mean 55.5)	161 Pakistan (men & women, mean 41.7)	100% Immigrants	75.30	28.40
Brock et al., 2007 [49]	Cross-sectional	57 Single arm	Australia	57 Vietnamese (females & males, elderly)	100% Immigrants	NA	35.10
Reed et al., 2007 [50]	Cross-sectional	71 Single arm	USA	71 East African (females, mean 44.1)	80% Immigrants	NA	36.47 $
Meyer et al., 2007 [51]	Cross-sectional	242 Single arm	Norway	242 Sri Lankan (men & women, range 31-60)	100% Immigrants	NA	31.50

Solanellasa et al., 2008 [52]	Cross-sectional	94 Comparison	35 Spain (females, mean 33.4 ± 7.8)	59 South America, Middle East, Maghreb, Europe, Philippines, Indian subcontinent, others (females, mean 33.4 ± 7.8)	100% Immigrants	35.94	34.44 $
Araujo et al., 2008 [53]	Cross-sectional	358 Single arm	USA	358 Puerto Rican, Dominican, Central American, South American. (males, mean 49.2 ± 11.5)	95% Immigrants	NA	87.63 $
Moreno-Reyes et al., 2009 [54]	Cross-sectional	400 Comparison	100 Belgium (females & males, mean 52 ± 6)	300 Congolese, Moroccan, Turkish, (females & males, mean 49 ± 5)	100% Immigrants	48.90	31.94
Madar et al., 2008 [55]	Cross-sectional	Single arm 80	Norway	80 Pakistani, Turkish, Somali (females, mean 28.1 ± 5.2)	> 80% Immigrants	NA	25.80
Benitez-Aguirre et al., 2009 [56]	Cohort interventional study	91 Single arm	Australia	91 North African (Sudan, Egypt, Kenya) (females &males, median (range) 11.5 (3-62))	100% Refugee	NA	27.50
Renzaho et al., 2011 [57]	Cross-sectional	49 Single arm	Australia	49 African (Ethiopia, Sudan, Eritrea, Somali, Ghana, Rwanda, Nigeria) (female & males, mean 41.5)	100% Immigrants & Refugees	NA	27.30
Sheikh et al., 2011 [58]	Retrospective study	215 Single arm	Australia	215 East Africa, Central Africa, West Africa, (females & males, mean 8 ± 4)	> 80% Refugees	NA	46.00
Gray et al., 2012 [59]	Cross-sectional	328 Single arm	Australia	328 Refugees (females & males, mean 7.8)	> 95% Refugees	NA	40.8
Andersson et al., 2013 [60]	Cross-sectional	61 Comparison	30 Sweden (females, mean age 42)	31 Middle east and Africa, (female, mean 35)	100% Immigrants	55.70	21.90*
Eggemoen et al., 2013 [61]	Cross-sectional	591 Single arm	Norway	591 South Sahara Africa, Middle east, North Africa, South Asia, East Asia, others (females & males, mean 22.7 ± 14.6)	100% Immigrants	NA	39.38*
Aucoin et al., 2013 [62]	Cross-sectional	1217 Single arm	Canada	1217 Africa, Asia, middle east, South America, others (children &women, range 0-45)	100% Refugees	NA	52.00
Campagna et al., 2013 [63]	Cross-sectional	1529 Comparison	151 USA (females & males, adults)	1378 East Africa (Eritrea, Ethiopia, Kenya, Somalia, Uganda, Burundi), Eastern Europe (Russia, Bulgaria), Southeast Asia (Burma, Cambodia, Laos, Philippines, Thailand, Vietnam), West Africa (Ghana, Guinea, Liberia, Mali, Nigeria, Sierra Leone). Others (Southern Asia (Bangladesh, Bhutan, India, Pakistan), Middle Africa (Cameroon), Eastern Asia (China, Korea), North Africa (Egypt, Morocco, Sudan), Central America (El Salvador, Mexico)	100% Immigrants & Refugees	62.40	46.8* $

				(females & males, adults)			
Vatanparast et al., 2013 [64]	Cross-sectional survey	> 72 [@] Comparison	# Canada, (Boys & girls, range 6-11)	72 Southeast Asia, Africa, Middle East, Latin America. (boys & girls, mean 8.9 ± 1.5)	100% Immigrants & Refugees	76.20	51.10
Sanati pour et al., 2014 [65]	Cross-sectional	92 Single arm	Australia	92 Afghan (female & male, mean 22.6 ± 11.9)	100% Refugees	NA	49.60
Demeke et al., 2015 [66]	Cross-sectional	67 Single arm	Sweden	67 Somali (females, mean 35.1 ± 9.2)	100% Immigrants	NA	22.40
Thoreson et al., 2015 [67]	Cohort	186 Single arm	USA	186 West, Central, and East African And sub-Saharan African, (females & males, mean 38 ± 10)	> 80% Immigrants	NA	54.40 [$]
Wai Man et al., 2016 [39]	Observational study	418 Single arm	Netherland	418 China (men & women, mean 56.3 ± 12)	86.5% Refugees	NA	45.60**
Osmancevic et al., 2016 [68]	Randomized trial	114 Single arm	Sweden	114 Somali (females, mean 34)	> 80% Immigrants	NA	21.24*
Afona et al., 2017 [69]	Cross-sectional	107 Single arm	Switzerland	107 Eritrean (females & males, aged ≥16)	100% Refugees	NA	33.13*
Taseen et al., 2017 [70]	Cross-sectional	138 Single arm	Canada	138 Refugees (females & males, mean 9.5)	100% Refugees	NA	55.10
Beukeboom et al., 2018 [71]	Cross-sectional retrospective	116 Single arm	Canada	116 Iraq, Somalia, Myanmar, Afghanistan (females & males, aged ≤ 16)	> 80% Refugees	NA	47.60
Adebayo et al., 2020 [72]	Cross-sectional	1686 Comparison	798 Finland, (females & males, range 30-64)	888 Russians, Somalis, Kurds, Finns, (females & males, range 18–64)	100% Immigrants	64.00	47.95
Yousef et al., 2021 [73]	Cross-sectional survey	11579 Comparison	9543 Canada (females & males, (SE) 37.51 (0.26))	153 countries & 13 ethnicities 2036, (females & males, mean (SE) 45.17 (0.58)	100% Immigrants	62.72	51.23

* Median converted to mean; ** Median (data insufficient to convert median to mean); [$] Values converted from ng/mL to nmol/L; [@] number of immigrants from survey data was not given; [#] sample size not given

Discussion

The results of this systematic review and meta-analysis confirmed the wide spectrum of lower concentration levels of S-25(OH)D among first-generation immigrants compared with the native-born populations in several host countries. Research evidence suggests the presence of significant differences in sociocultural contexts and various outcomes between first-generation and second- or third-generation immigrants [74, 75]. Moreover, researchers recommended studying and comparing ethnic groups from the same generation [74-76]. Previous systematic reviews on vitD included immigrant populations from aggregated generations (first, second, or more generations), resulting in high heterogeneity in the study population. This study reported and compared vitD levels from studies that included at least 80% first-generation immigrants.

In our systematic review, we observed significant variations in the age and sex of studies' participants, the origin of immigrants and their length of stay in the host country. S-25(OH)D concentration was measured during different seasons of the year. Moreover, variation was also observed in the assay methodology used to measure S-25(OH)D between included studies. This suggests standardized measurement of S-25(OH)D data may enable comparison of S-25(OH)D concentration levels and assist in estimating the prevalence of deficiency/insufficiency of S-25(OH)D in various regions of the world.

Our study had some strengths and limitations. Unlike previous systematic reviews, using results for first-generation immigrants only was considered unique to this study. Moreover, including studies from languages other than English ensured the results were globally inclusive. Because of the complex bidirectional association between S-25(OH)D and chronic diseases, we excluded studies that included more than 20% unhealthy populations with disorders that might impact S-25(OH)D concentration levels (e.g., osteoporosis). Although this deviation from the study protocol

might have introduced selection bias and outcome reporting bias, we included healthy people to avoid the clinical impact of any disorders on concentration levels of S-25(OH)D and minimize heterogeneity across the included studies.

Conclusion

This study offers novel findings pertaining global S-25(OH)D among first-generation immigrants. First-generation immigrants have lower S-25(OH)D than non-immigrants. Developing an international immigrant guideline to integrate and implement strategies for vitD improvement may be warranted. This study is in progress and all results presented here were based on the studies currently included (N=35).

References

1. Erdman, P., et al., *CAP Laboratory Improvement Programs Accuracy-Based Vitamin D Survey Six Years of Quality Improvement Guided by Proficiency Testing.* Arch Pathol Lab Med, 2019. **143**.
2. Spedding-Simon, *Vitamin D and Human Health*. 2015 ed. 2015, MDPI • Basel • Beijing • Wuhan: Publisher Shu-Kun Lin.
3. Wacker, M. and M.F. Holick, *Vitamin D—Effects on Skeletal and Extraskeletal Health and the Need for Supplementation.* Nutrients, 2013. **5**: p. 111-148.
4. Autier, P., *Vitamin D status as a synthetic biomarker of health status.* Endocrine, 2016. **51**(2): p. 201-202.
5. Chiu, M., et al., *Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-ethnic Study.* Canadian Journal of Cardiology, 2012. **28**(1): p. 20-26.
6. Health Canada, *Canadian Research on Immigration and Health.* Health Canada, Cat. No H21- 149/1999E, 1999.
7. Mithal, A., et al., *Global vitamin D status and determinants of hypovitaminosis D*, in *Osteoporosis International*. 2009, Springer London. p. 1807-1820.
8. Lips, P., et al., *Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society*. European journal of endocrinology, 2019. **180**(4): p. P23-P54.
9. Vieth, R., *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml).* Best Practice & Research Clinical Endocrinology & Metabolism, 2011. **25**: p. 681-691.
10. Ross A. Catharine, et al., *DIETARY REFERENCE INTAKES Calcium Vitamin D Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board*. 2011.
11. Dawson-Hughes, B., *Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment - UpToDate*. 2021.
12. Heaney, R.P., *Vitamin D in Health and Disease.* Clinical Journal of the American Society of Nephrology, 2008. **3**(5): p. 1535-1541.
13. Robyn, L. and N. Rachel, *What is the optimal level of vitamin D? Separating the evidence from the rhetoric clinical*. 2014.
14. Sohl, E., et al., *Thresholds for Serum 25(OH)D Concentrations With Respect to Different Outcomes.* J Clin Endocrinol Metab, 2015. **100**: p. 2480-2488.
15. Bischoff-Ferrari, H.A., et al., *Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes.* The American journal of clinical nutrition, 2006. **84**(1): p. 18-28.

16. Thuesen, B., et al., *Determinants of vitamin D status in a general population of Danish adults.* Original Full Length Article, 2011.

17. Renzaho, A.M.N., J.A. Halliday Bhsci, and C. Nowson, *Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review.* Nutrition, 2011. **27**: p. 868-879.

18. Statistics Canada, *Vitamin D blood levels of Canadians*. 2015.

19. Martin, C.A., U. Gowda, and A.M.N. Renzaho, *The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis.* Nutrition, 2016. **32**: p. 21-32.

20. Palacios, C. and L. Gonzalez, *Is vitamin D deficiency a major global public health problem?* Journal of Steroid Biochemistry and Molecular Biology, 2014. **144**: p. 138-145.

21. Holick, M.F., *The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health INTRODUCTION: HISTORICAL PERSPECTIVE.* Public Health Reviews, 2010. **32**(1): p. 267-283.

22. Spiro, A. and J.L. Buttriss, *Vitamin D: An overview of vitamin D status and intake in Europe.* Nutrition Bulletin, 2014. **39**(4): p. 322-350.

23. Charoenngam, N., A. Shirvani, and M.F. Holick, *Vitamin D for skeletal and non-skeletal health: What we should know.* Journal of Clinical Orthopaedics and Trauma, 2019. **10**(6): p. 1082-1093.

24. Zmijewski, M.A., *Vitamin D and Human Health.* International Journal of Molecular Sciences, 2019. **20**(1): p. 145.

25. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British Journal of Nutrition, 2014. **111**: p. 23-45.

26. Granlund, L., et al., *Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden.* European Journal of Clinical Nutrition, 2016. **70**(3): p. 373-379.

27. Benson, J. and S. Skull, *Hiding from the sun - vitamin D deficiency in refugees.* Aust Fam Physician. , 2007. **36**(5): p. 355-7.

28. Yousef, S., G.A. Wells, and J. Elliott. *Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis. PROSPERO (CRD42018086729)*. 2018.

29. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis.* Systematic Reviews, 2019. **8**(1): p. 1-6.

30. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3*. 2022 February 2022 [cited October 2022 8]; Available from: www.training.cochrane.org/handbook.

31. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Annals of internal medicine, 2009. **151**(4): p. 264-269.

32. McGowan, J., et al., *PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement.* Journal of Clinical Epidemiology, 2016. **75**: p. 40-46.

33. Adit A. Ginde, Mark C. Liu, and Carlos A. Camargo Jr, *Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988–2004.* Arch Intern Med, 2009. **169**(6): p. 626–632-626–632.

34. McGrath, S., et al., *Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis.* Statistical methods in medical research, 2020. **29**(9): p. 2520-2537.

35. Wan, X., et al., *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.* BMC medical research methodology, 2014. **14**(1): p. 1-13.

36. NHLBI-NIH. *Quality assessment tool for observational cohort and cross-sectional studies –NHLBI, NIH [homepage on the Internet]*. 2021 July, 2021; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

37. Man, P.W., et al., *Vitamin D status in the Chinese population in the Netherlands: The DRAGON study.* The Journal of Steroid Biochemistry and Molecular Biology, 2016. **164**: p. 194-198.

38. Stephens, W.P., et al., *Observations on the Natural History of Vitamin D Deficiency amongst Asian Immigrants.* QJM: An International Journal of Medicine, 1982. **51**(2): p. 171-188.

39. Brunvand, L. and E. Haug, *Vitamin D deficiency amongst Pakistani women in Oslo.* Acta obstetricia et gynecologica Scandinavica, 1993. **72**(4): p. 264-268.

40. Glerup, H., et al., *Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited.* Journal of internal medicine, 2000. **247**(2): p. 260-268.

41. Skull, S.A., et al., *Vitamin D deficiency is common and unrecognized among recently arrived adult immigrants from The Horn of Africa.* Internal Medicine Journal, 2003. **33**(1-2): p. 47-51.

42. Meyer, H.E., et al., *Vitamin D deficiency and secondary hyperparathyroidism and the association with bone mineral density in persons with Pakistani and Norwegian background living in Oslo, Norway: The Oslo Health Study.* Bone, 2004. **35**(2): p. 412-417.

43. Brock, K., et al., *Associations with vitamin D deficiency in "at risk" Australians.* The Journal of steroid biochemistry and molecular biology, 2004. **89**: p. 581-588.

44. Holvik, K., et al., *Prevalence and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: the Oslo Immigrant Health Study.* European journal of clinical nutrition, 2005. **59**(1): p. 57-63.

45. Nicolaidou, P., et al., *Low vitamin D status in preschool children in Greece.* Nutrition Research, 2006. **26**(12): p. 620-625.

46. Holvik, K., et al., *Pakistanis living in Oslo have lower serum 1, 25-dihydroxyvitamin D levels but higher serum ionized calcium levels compared with ethnic Norwegians. The Oslo Health Study.* BMC endocrine disorders, 2007. **7**(1): p. 1-6.

47. Brock, K., et al., *Effects of diet and exercise on plasma vitamin D (25 (OH) D) levels in Vietnamese immigrant elderly in Sydney, Australia.* The Journal of steroid biochemistry and molecular biology, 2007. **103**(3-5): p. 786-792.

48. Reed, S.D., et al., *Prevalence of vitamin D insufficiency and clinical associations among veiled East African women in Washington State.* Journal of Women's Health, 2007. **16**(2): p. 206-213.

49. Meyer, H.E., et al., *Vitamin D status in sri lankans living in sri lanka and norway.* British journal of nutrition, 2008. **99**(5): p. 941-944.

50. González Solanellas, M., et al., *Deficiencia de vitamina D en mujeres en edad fértil.* Atención primaria, 2008. **40**(8): p. 393-399.

51. Araujo, A.B., et al., *Serum 25-hydroxyvitamin D and bone mineral density among Hispanic men.* Osteoporosis international, 2009. **20**(2): p. 245-255.

52. Moreno-Reyes, R., et al., *Vitamin D deficiency and hyperparathyroidism in relation to ethnicity: a cross-sectional survey in healthy adults.* European journal of nutrition, 2009. **48**(1): p. 31-37.

53. Madar, A.A., L.C. Stene, and H.E. Meyer, *Vitamin D status among immigrant mothers from Pakistan, Turkey and Somalia and their infants attending child health clinics in Norway.* British journal of nutrition, 2008. **101**(7): p. 1052-1058.

54. Benitez-Aguirre, P.Z., et al., *The natural history of vitamin D deficiency in African refugees living in Sydney.* Medical journal of Australia, 2009. **190**(8): p. 426-428.

55. Renzaho, A.M., et al., *Prevalence of vitamin D insufficiency and risk factors for type 2 diabetes and cardiovascular disease among African migrant and refugee adults in Melbourne.* Asia Pacific journal of clinical nutrition, 2011. **20**(3): p. 397-403.

56. Sheikh, M., et al., *Vitamin D deficiency in refugee children from conflict zones.* Journal of Immigrant and Minority Health, 2011. **13**(1): p. 87-93.

57. Gray, K., et al., *Vitamin D and tuberculosis status in refugee children.* The Pediatric infectious disease journal, 2012. **31**(5): p. 521-523.

58. Andersson, Å., et al., *Vitamin D intake and status in immigrant and native Swedish women: a study at a primary health care centre located at 60 N in Sweden.* Food & Nutrition Research, 2013. **57**(1): p. 20089.

59. Eggemoen, Å.R., et al., *Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults.* BMJ open, 2013.

60. Aucoin, M., et al., *Vitamin D status of refugees arriving in Canada Findings from the Calgary Refugee Health Program.* Can Fam Physician 2013. **59**: p. 188-94.

61. Campagna, A.M., et al. *Effect of country of origin, age, and body mass index on prevalence of vitamin D deficiency in a US immigrant and refugee population*. in *Mayo Clinic Proceedings*. 2013. Elsevier.

62. Vatanparast, H., C. Nisbet, and B. Gushulak, *Vitamin D insufficiency and bone mineral status in a population of newcomer children in Canada.* Nutrients, 2013. **5**(5): p. 1561-1572.

63. Sanati Pour, M., et al., *Prevalence of dyslipidaemia and micronutrient deficiencies among newly arrived Afghan refugees in rural Australia: a cross-sectional study.* BMC Public Health, 2014. **14**(1): p. 1-8.

64. Demeke, T., et al., *Lower bone mineral density in Somali women living in Sweden compared with African–Americans.* Archives of osteoporosis, 2015. **10**(1): p. 1-5.

65. Thoreson, C.K., et al., *Biochemical and clinical deficiency is uncommon in African immigrants despite a high prevalence of low vitamin D: the Africans in America study.* Osteoporosis International, 2015. **26**(11): p. 2607-2615.

66. Osmancevic, A., et al., *Vitamin D treatment in Somali women living in Sweden–Two randomized, placebo-controlled studies.* Clinical endocrinology, 2016. **85**(4): p. 535-543.

67. Chernet, A., et al., *Serum 25-hydroxyvitamin D levels and intramuscular vitamin D3 supplementation among Eritrean migrants recently arrived in Switzerland.* Swiss medical weekly, 2017. **147**.

68. Taseen, K. and G. Beaulieu, *Vitamin D levels and influencing predictors in refugee children in Sherbrooke (Quebec), Canada.* Paediatrics & Child Health, 2017. **22**(6): p. 307-311.

69. Beukeboom, C. and N. Arya, *Prevalence of nutritional deficiencies among populations of newly arriving government assisted refugee children to Kitchener/Waterloo, Ontario, Canada.* Journal of Immigrant and Minority Health, 2018. **20**(6): p. 1317-1323.

70. Adebayo, F.A., et al., *Prevalence and determinants of vitamin D deficiency and insufficiency among three immigrant groups in Finland: evidence from a population-based study using standardised 25-hydroxyvitamin D data.* Public health nutrition, 2020. **23**(7): p. 1254-1265.

71. Yousef, S., et al., *Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey.* Nutrients, 2021. **13**(8): p. 2702-2702.

72. Salant, T. and S.L. Diane, *Measuring culture: a critical review of acculturation and health in Asian immigrant populations.* Social Science & Medicine, 2003. **71**: p. 71-90.

73. Zhu, L., *Depression risks and correlates among different generations of Chinese Americans: The effects of relationships with friends and relatives.* Social Sciences, 2017. **6**(2).

74. Stern, P.J., *Generational Differences.* The Journal of hand surgery 2002. **27**(2): p. 187-94.

5.3 Global vitD maps for immigrants compared with non-immigrants

Section overview

This section is a continuation of our previous two sections (5.1 and 5.2). In this section, the initial findings of section 5.2 were used to develop global maps (sample maps) for S-25(OH)D levels among immigrants compared with non-immigrants based on the region and country of the host population. Therefore, section 5.2, including method and results, is the reference document for these maps.

Manuscript status

This manuscript is in preparation.

Said Yousef*, Lamia Hayawi; Maleka Ben Mahdi; Alomgir Hossain; Douglas Manuel; Manny Papadimitropoulos; Ian Colman; MoezAlIslam Faris; George A Wells

Author roles and contributions

YS, MD, CI, PM, HA, and GW conceived the study. YS, HL screened and selected the included studies. YS and MBM performed the data extraction. YS and HL working on the analysis and preparing the results for the manuscripts. YS created the sample maps and drafted the current manuscript.

Mapping global S-25(OH)D levels among first-generation immigrants from different origins compared to native-born population.

Said Yousef*; Lamia Hayawi; Maleka Ben Mahdi; Manny Papadimitropoulos; Ian Colman; Alomgir Hossain; Douglas Manuel; MoezAlIslam Faris; George A Wells

Corresponding author*

*Said Yousef, MSc.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7

Lamia Hayawi, MD, MSc.
Children's Hospital of Eastern Ontario Research Institute,
Ottawa, ON, Canada
lhayawi@cheo.on.ca

Maleka Ben Mahdi
The Gray Clinic, Fraser Health
22722 Lougheed Hwy, Maple Ridge, BC V2x 2v6
M.mahdi@zu.edu.ly

Manny Papadimitropoulos, Ph.D.
Health Outcomes Scientific Leader, Latin America, GPORWE International (Latin America, Immunology), Eli Lilly Canada Inc.
3650 Danforth Avenue, Toronto ON M1N 2E8
Assistant Professor, University of Toronto, Faculty of Pharmacy, Toronto, ON, Canada
manny_p@lilly.com

Ian Colman, Ph.D.
School of Epidemiology and Public Health, University of Ottawa,
600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
icolman@uottawa.ca

Alomgir Hossain, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
alhossain@ottawaheart.ca

Douglas Manuel, MD, MSc
Institute for Clinical Evaluative Sciences, Ottawa Hospital, Civic Campus
1053 Carling Avenue, Box 684, Administrative Services Building,
1st Floor, Ottawa, Ontario K1Y 4E9
dmanuel@ohri.ca

MoezAlIslam Faris, Ph.D.
Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE
mfaris@sharjah.ac.ae

George A Wells, Ph.D.
School of Epidemiology and Public Health, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Canada, K1G 5Z3
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Canada, K1Y4W7
gawells@ottawaheart.ca

An outline of the proposed manuscript is provided. It will be completed once the systematic review and meta-analysis is updated and final maps generated.

Research objective

We aimed in this section to visualize the results of the systematic review and meta-analysis (section 5.2) in mapping format. These maps were developed to show the global distribution of immigrants and to compare S-25(OH)D levels among immigrants with non-immigrants based on the region, country of the host population, and the migration point to the host country.

Method

We followed the WHO recommendations for monitoring migrants' health by collecting and mapping comparable data [1]. This is a continuous work of the two previous sections (5.1 and 5.2). The method and results described in section 5.2 are the baseline information for this section. The results of section 5.2 were presented in tabular format; consequently, the same findings were used to establish global maps (sample maps) for S-25(OH)D levels of immigrants and non-immigrants in different geographical regions.

We used ArcGIS software to illustrate the global vitD data. ArcGIS software is a geographical information system (GIS) that allows for managing and analyzing geographic data by visualizing geographical statistics through maps [2]. This thesis's mapping method is unique to chapter 5 only (section 5.1-5.3).

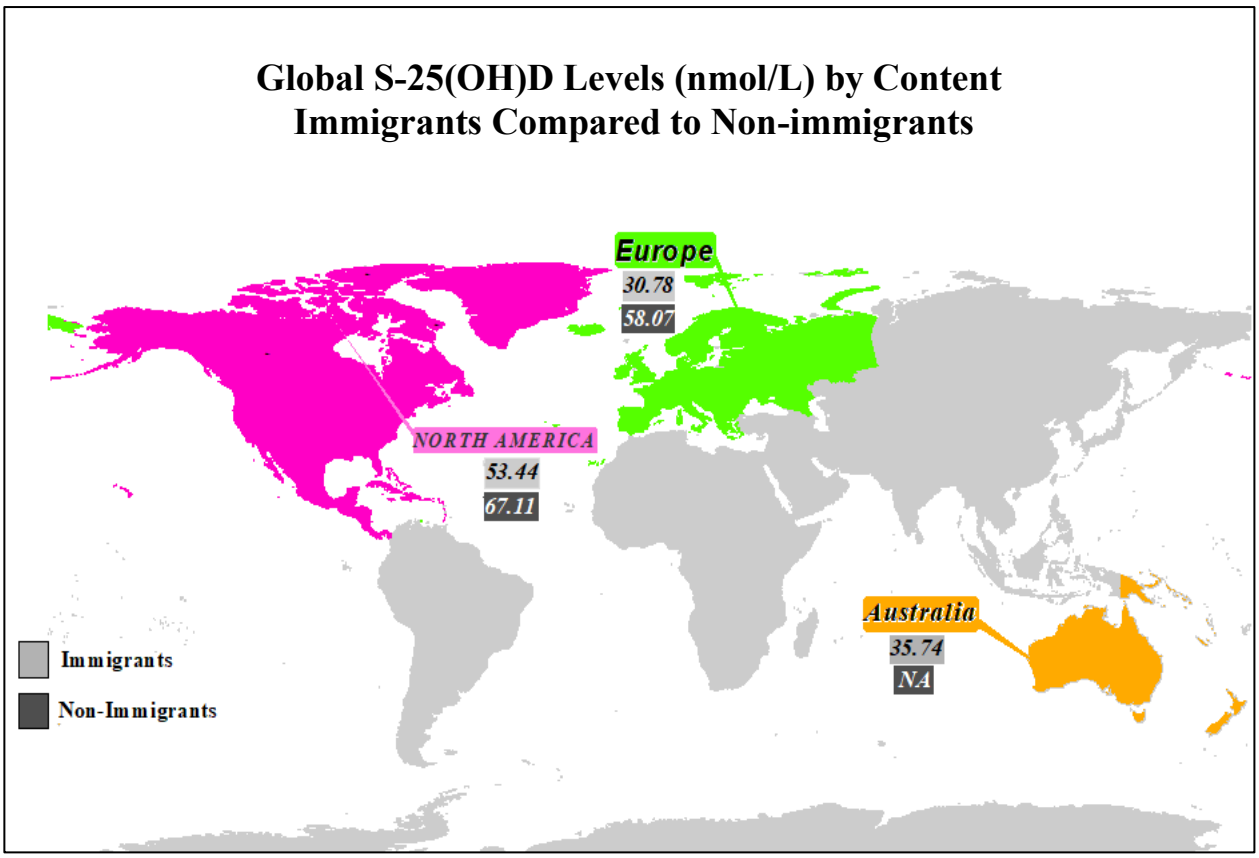
Results

Some initial example maps

The figures below (Fig.1-7) are sample thematic maps that visually represent one or more specific data topics in standard regional and/or global geographic areas. The mean concentration levels of S-25(OH)D were estimated based on the initial results of the systematic review (section 5.2).

The mapping structure is exclusive to the findings of this systematic review. It will be used to present the final global maps when the search update is completed and related data extracted.

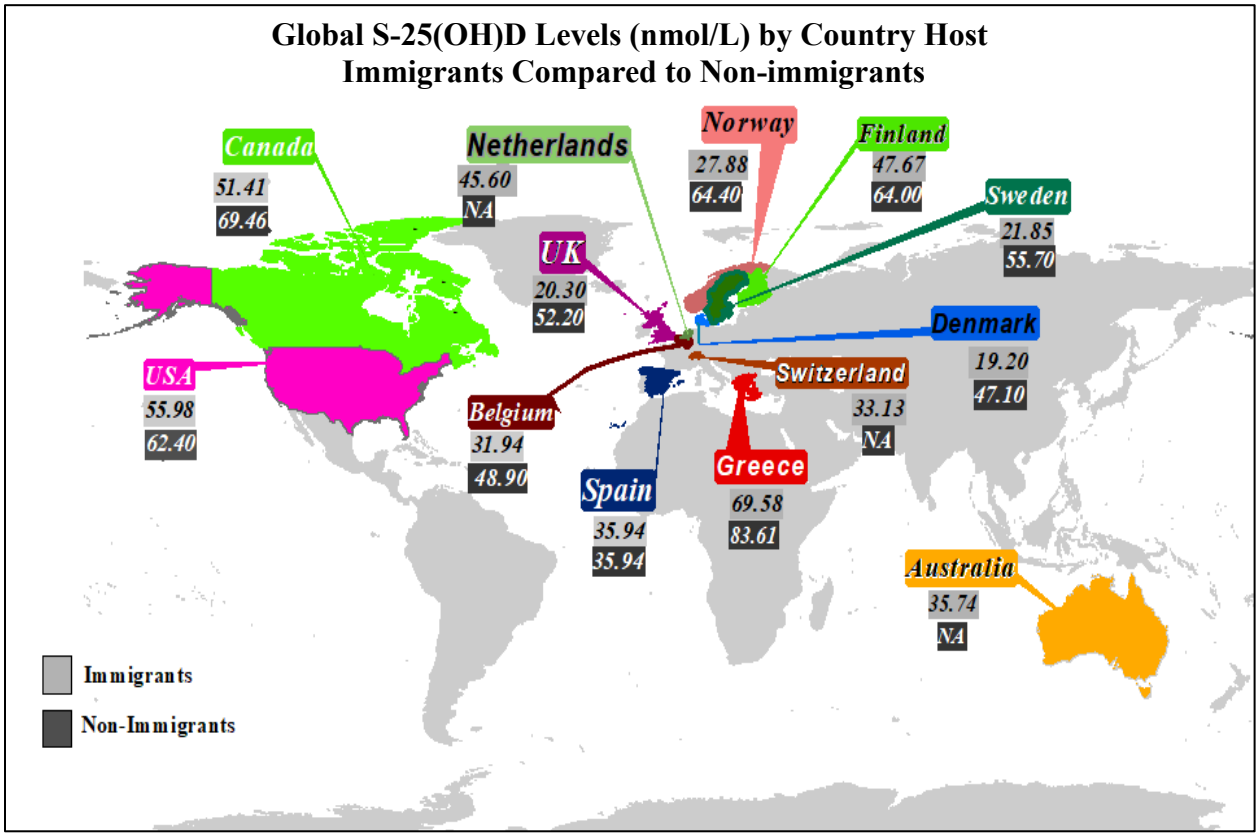
Fig.1. Global S-25(OH)D levels (nmol/L) by content for immigrants compared to Non-immigrants



NA: Data not available or the included studies were single arm studies.

This figure shows the pooled estimated mean levels of S-25(OH)D for immigrants (light gray) compared to non-immigrants (dark gray) based on the three continents of North America, Europe, and Australia. The included studies from Australia were single-arm studies, in which S-25(OH)D for non-immigrants was not given.

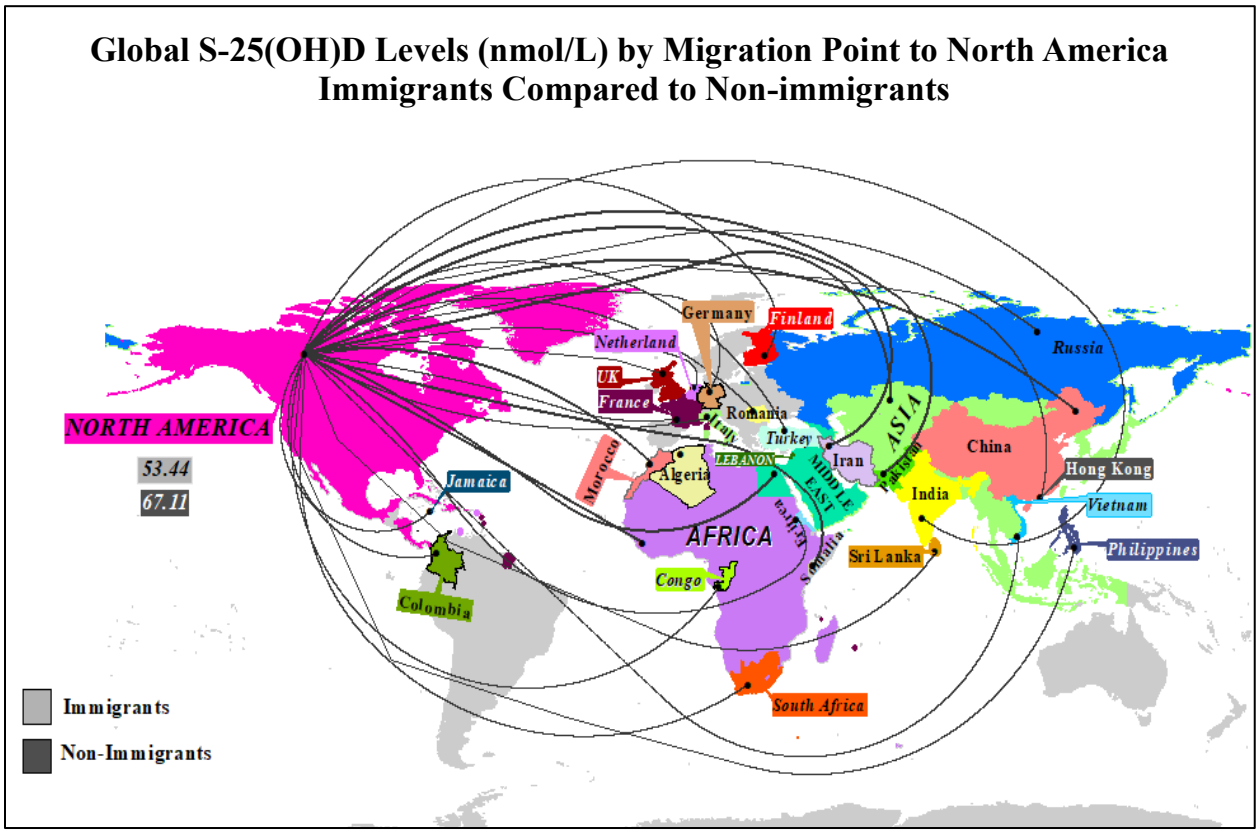
Fig. 2. Global S-25(OH)D levels (nmol/L) by country host for immigrants compared to Non-immigrants.



NA: Data not available or the included studies were single arm studies.

This figure shows the pooled estimated mean levels of S-25(OH)D for immigrants (light gray) compared to non-immigrants (dark gray) for the thirteen host countries.

Fig. 3. Global S-25(OH)D levels (nmol/L) by migration point to North America for immigrants compared to Non-immigrants

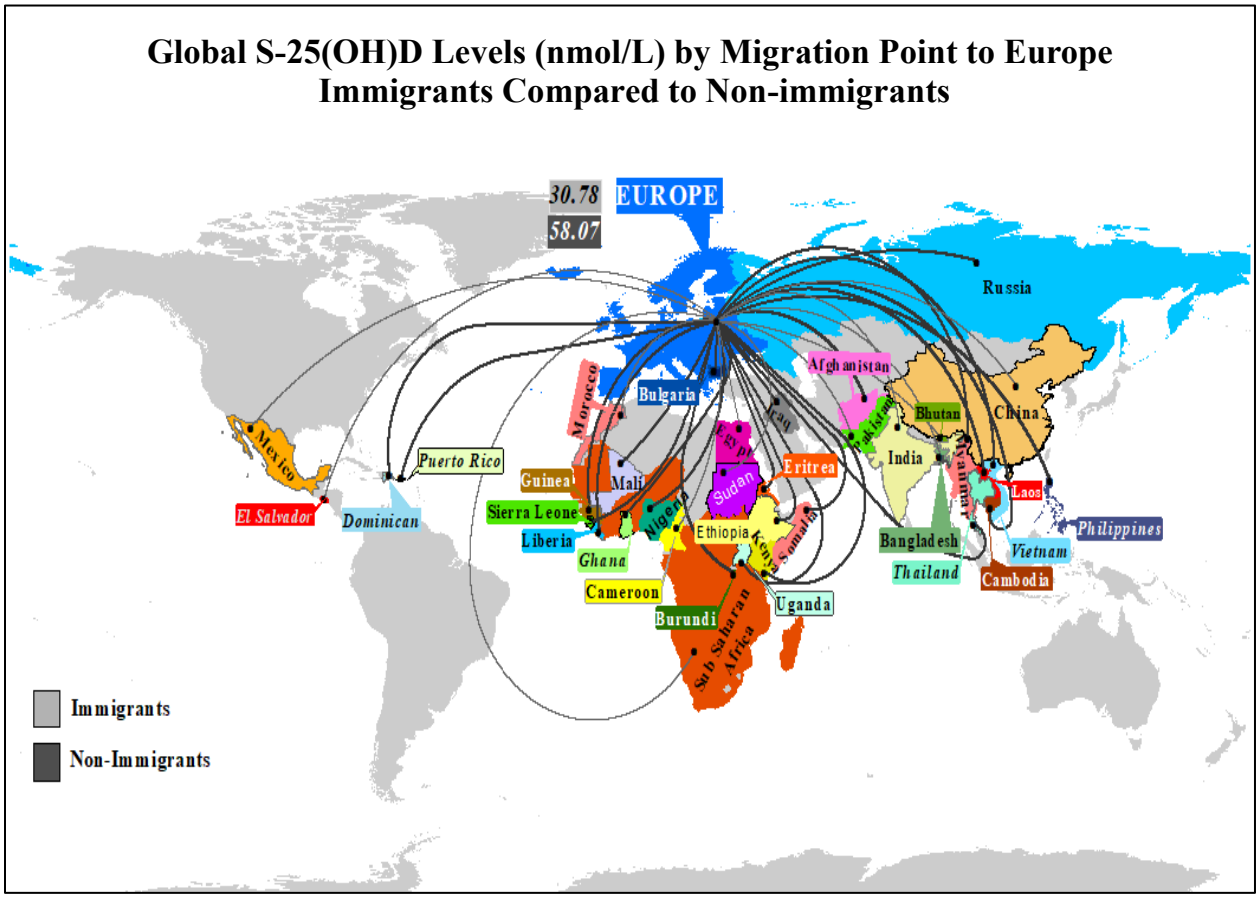


NA: Data not available or the included studies were single arm studies.

Darker lines indicate larger sample size

Figure 3 shows the migration points to north America. The darker lines indicate a larger sample size contributing more to the pooled estimated mean levels of S-25(OH)D for immigrants (light gray) compared to non-immigrants (dark gray).

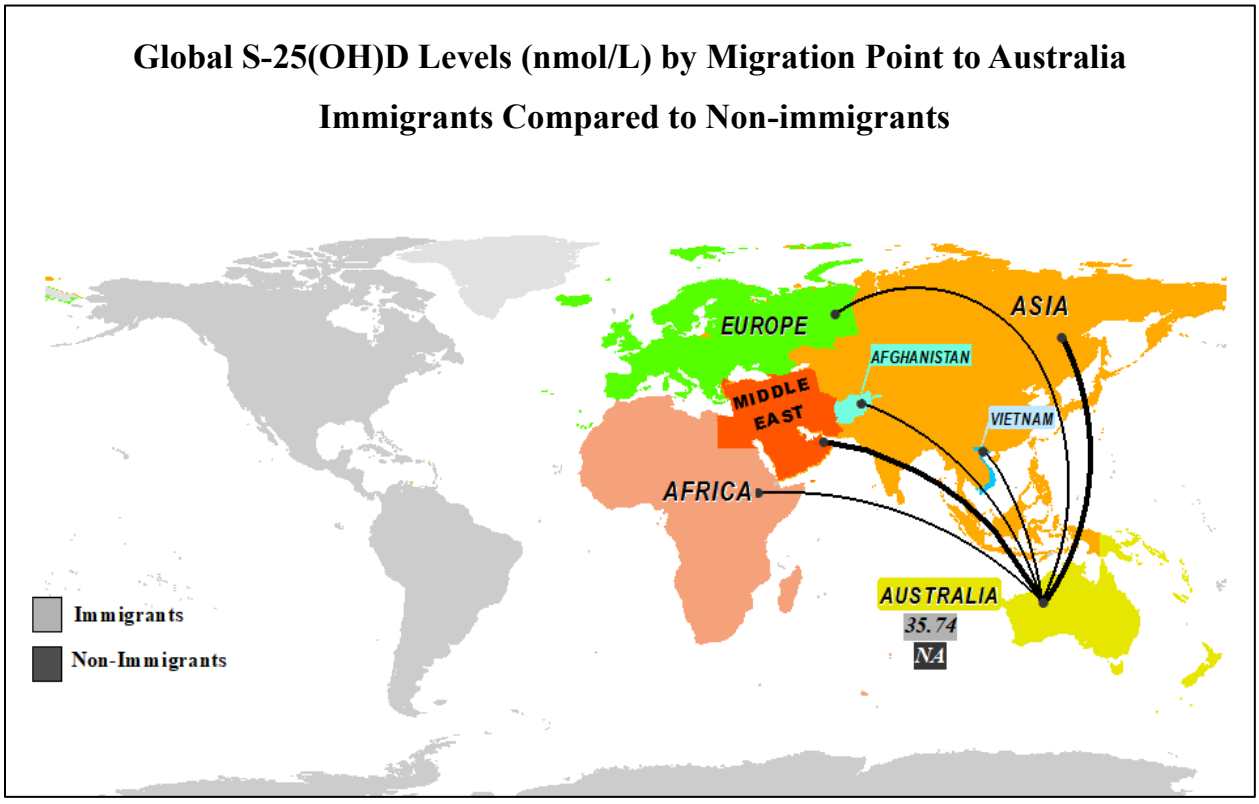
Fig. 4. Global S-25(OH)D levels (nmol/L) by Migration Point to Europe for immigrants compared to Non-immigrants.



Darker lines indicate larger sample size

Figure 4 shows the migration points to Europe. The darker lines indicate a larger sample size contributing more to the pooled estimated mean levels of S-25(OH)D for immigrants (light gray) compared to non-immigrants (dark gray).

Fig. 5. Global S-25(OH)D levels (nmol/L) by country for immigrants compared to Non-immigrants.

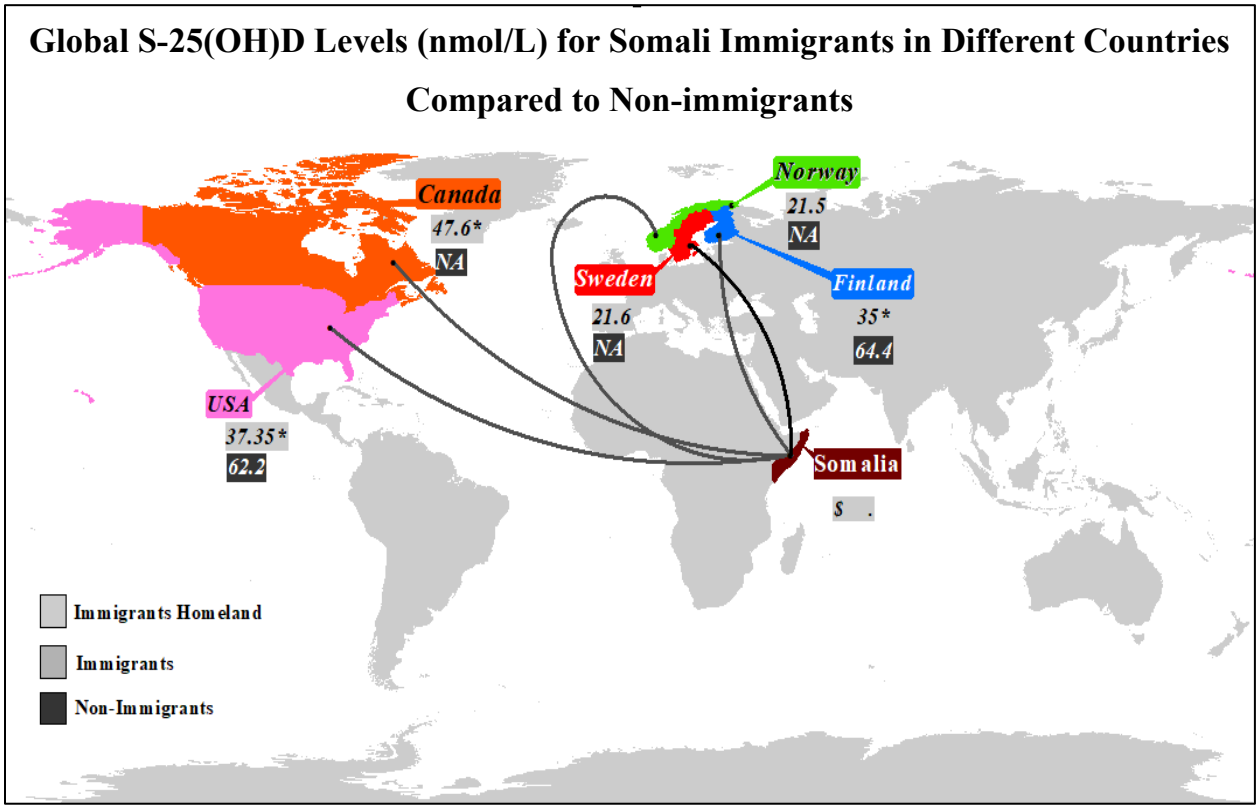


NA: Data not available or the included studies were single arm studies.

Darker lines indicate larger sample size

Figure 5 shows the migration points to Australia. The darker lines indicate a larger sample size contributing more to the pooled estimated mean levels of S-25(OH)D for immigrants (light gray). The included studies were single-arm studies, in which S-25(OH)D for non-immigrants (dark gray) was not given.

Fig. 6. Global S-25(OH)D levels (nmol/L) for Somali immigrants in different countries compared to non-immigrants.



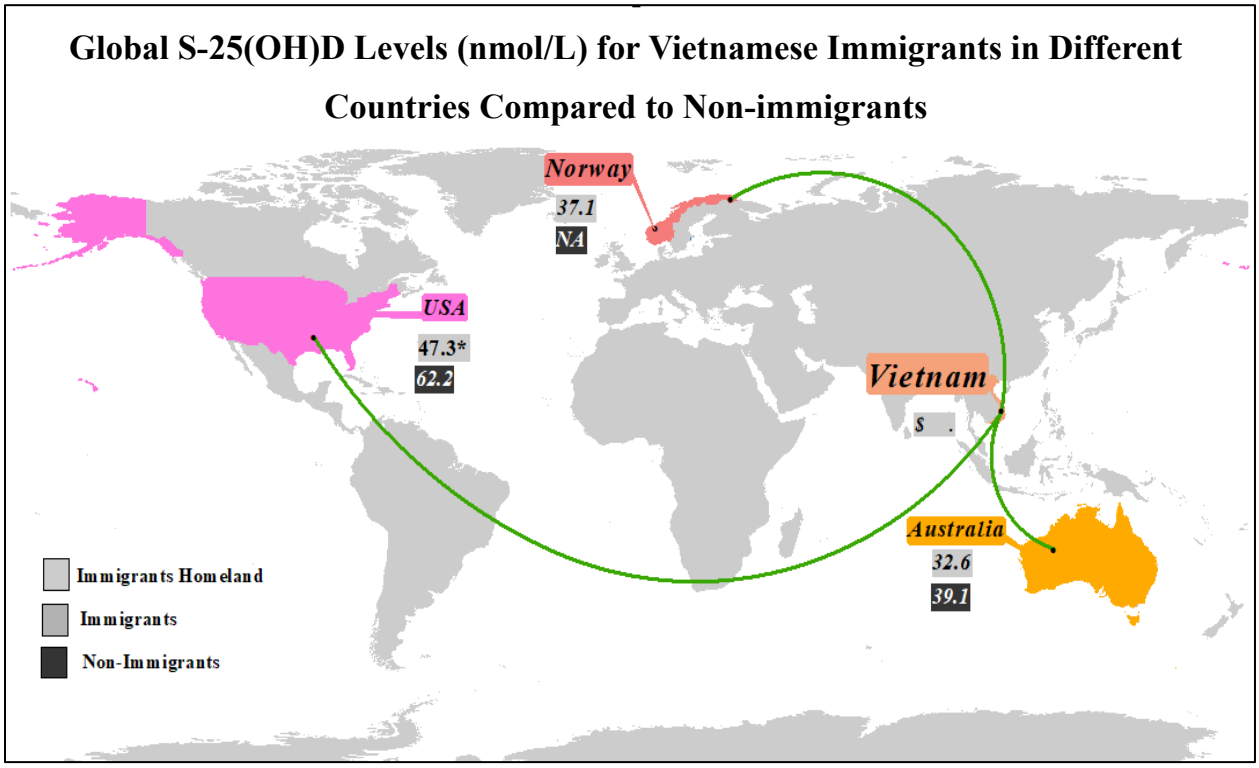
NA: Data not available or the included studies were single arm studies.

* Value of S-25(OH)D levels (nmol/L) for group of immigrants (not limited to Somali)

$ Value of S-25(OH)D levels (nmol/L) for Somali in Somalia. Data not available.

Immigrants moved from Somalia to different host countries, and the pooled estimated mean levels of S-25(OH)D for Somalian immigrants (light gray) compared to the non-immigrants (dark gray) in the host countries are shown in Figure 6. The S-25(OH)D level for the Somalian population in Somalia was unavailable.

Fig. 7. Global S-25(OH)D levels (nmol/L) for Vietnamese immigrants in different countries compared to non-immigrants.



NA: Data not available or the included studies were single arm studies.

* Value of S-25(OH)D levels (nmol/L) for group of immigrants (not limited to Vietnamese)

$ Value of S-25(OH)D levels (nmol/L) for Vietnamese in Vietnam in 2011 (80.5 nmol/L; Males 91·9; female 75·1) [3].

Immigrants moved from Vietnam to different host countries and the pooled estimated mean levels of S-25(OH)D for Vietnamese immigrants (light gray) compared to the non-immigrants (dark gray) in the host countries are shown in Figure 6. The S-25(OH)D level for the Vietnamese population in Vietnam was cited from a systematic review (80.5 nmol) [3].

Discussion

Data visualization by presenting the key findings in standard global geographic areas is a tool that makes statistical information more comparable, more interpretable, and easy to identify relationships.

The discussion and interpretation of the maps will be available based on the final finding of the updated systematic review and meta-analysis. The focus will be given to the distribution of immigrants in different countries and regions. Comparing immigrants to non-immigrants based on the host country or region, the movement points, and the latitude will be discussed. Moreover, immigrants in a host country (e.g., Somalian in Canada) will be compared to the same immigrants in another host country (e.g., Somalian in US), and to Somalian people living in Somalia.

References

1. WHO, *Report on the health of refugees and migrants in the WHO European region: no public health without refugee and migrant health.* 2018.
2. Kholoshyn, I., et al., *Cloud ArcGIS Online as an innovative tool for developing geoinformation competence with future geography teachers.* arXiv preprint arXiv:1909.04388, 2019.
3. Hilger, J., et al., *A systematic review of vitamin D status in populations worldwide.* British Journal of Nutrition, 2014. **111**: p. 23-45.

Chapter 6: Discussion and conclusion

Chapter overview

Chapter 6 provides a brief overview and summary of the overall findings, identifies the rationale and novelty of this thesis, discusses the strengths and limitations associated with the three major studies (set out in Chapters 3, 4, and 5), and offers avenues and recommendations for further research.

6.1 Rationale and novelty of the thesis

The underlying rationale for this thesis was to answer the following research questions.

Question 1: What are the status and determinants explaining the variations in vitD among first-generation Canadian immigrants compared with non-immigrants? In addition, do the accumulated lower levels of vitD among immigrants explain their health deterioration after immigration?

Question 2: Do available CPGs follow established development criteria and acknowledge the growing problem of vitD deficiency among immigrants?

Question 3: What are the global status and determinants of vitD among first-generation immigrants compared with native-born people of the host country?

This thesis extensively examined the topic of vitD among immigrants. The three studies investigated different research questions that have not previously been explored in primary and secondary research. Therefore, several findings are considered novel contributions to this topic. These contributions are presented in Table 1.

Table 1: Summary of key contributions of this thesis

Chapter/ Section and Contribution area	Unique contribution
Chapter 3.1–3.3 **CHMS data**	• Use of large national data on vitD and immigrants. • Examination of comprehensive clinical, physical, and biological measures, along with self-reported health data. • The data reflect the ethnocultural diversity of immigrants from more than 153 countries and represent more than 13 major ethnic groups. • This study focused on first-generation immigrants. Previous immigration studies recommended assessing vitD status and its determinants among subgroups living in the same country and comparing the same generation of immigrants rather than considering aggregated generations. • The data were validated against other datasets (e.g., Canadian Community Health Survey, Census data, and the 2011 National Household Survey).
Chapter 3.1–3.3	• The results of this chapter were based on a high-quality population-based national survey that is conducted every 2 years with appropriate weighting to accurately represent all of Canada.
	• Ethnicity was the factor that predicted/explained variations in S-25(OH)D between immigrants and non-immigrants. This finding suggests there is genetic variation that warrants further investigation. • Levels of S-25(OH)D by region, country of birth, and ethnicity were given for immigrants. • The most deficient groups were those born in Morocco, India, and Lebanon compared with native-born Canadians; in terms of the ethnic background, vitD deficiency was highest among Japanese, Arab, and Southeast Asians compared with white ethnic groups.
The study findings	• The study examined skin melanin levels among immigrants compared with non-immigrants as a reliable skin pigmentation measure. • Differences in melanin were observed by region or country of birth and other sociodemographic factors. • No previous studies examined the relationship between melanin levels and S-25(OH)D among immigrants based on their ethnicity and region/country of birth compared with non-immigrants. • The relationship between vitD and melanin in the context of first-generation immigrants and essential factors related to immigrants have not fully been established or elucidated in the literature. • The use of indoor tanning has not previously been linked to S-25(OH)D, melanin, immigrants, and non-immigrants using large national data. • The present study was designed to fill this knowledge gap and explored whether melanin levels explained S-25(OH)D variations between immigrants and native-born Canadians. • This study offered novel findings, as no such study had previously been conducted.

	• Although the CHMS used a cross-sectional design, the prevalence of CDs has been used as a proxy indicator to verify the existence of the healthy immigrant effect and health deterioration over time in Canada. • The longer immigrants had lived in Canada (i.e., 5 and 10 years), the higher the prevalence of CDs, which may be considered an early sign of health deterioration. • Investigating immigrants' health deterioration in the context of vitD using CDs and related biomarkers as a proxy indicator is unique to this study • In addition to the changes in lifestyle and environment, the accumulated lower S-25(OH)D levels among immigrants may impact their health profile in terms of CD-related biomarkers, partially explaining immigrants' health deterioration over time.
Chapter 4.1–4.2 **Global vitD CPGs and immigrants' health CPGs**	• Although vitD deficiency among immigrants is a global issue that has been detected for more than five decades, this analysis showed that available CPGs for vitD and immigrants' health were country-specific and tended to be relatively poor in acknowledging the growing problem of vitD deficiency among immigrants. • In addition to most available guidelines not being identified as CPGs, few of these CPGs met the criteria for guideline development. • This study recommends developing national and international CPGs that respond to the growing problem of vitD deficiency among immigrants to reduce the gaps between research, policy, and practice concerning vitD and immigrants' health. • The findings on this topic have not been investigated in previous systematic reviews.
Chapter 5.1–5.2 **Global evidence on vitD and immigrants**	• Previous systematic reviews have not involved a global systematic review of vitD and first-generation immigrants. • This study followed the WHO recommendations for mapping immigrants' data. • Mapping vitD among immigrants has not been performed in previous systematic reviews. • This global systematic review investigated determinants of vitD deficiency among first-generation immigrants. • This section is in progress.
Chapters 3–5 **Overall findings**	• Protocol for a national CPG on immigrants' health and vitD. • Protocol for an international CPG on immigrants' health and vitD. • This section is not yet established.

6.2 Strengths and limitations

In this thesis, an analysis of a large national database (CHMS) and health technology assessment was undertaken. The strengths of each study (Chapters 3–5) were described (Table 1), followed by a discussion of the associated limitations.

Table 1. Strengths of the thesis

Chapter/section	Strengths
Chapter 3.1–3.3 **(CHMS data analysis)**	• In addition to being validated against other national data, the CHMS has several strengths. The CHMS provided the first national, comprehensive data and used several reliable clinical, physical, biological, and laboratory measures (including melanin measures) to overcome the limitations of self-reported data. The data represented the ethnocultural diversity of immigrants from over 150 countries and more than 13 major ethnic groups. Moreover, S-25(OH)D levels were collected over an entire year, which enabled adjustment for seasonal variations in UVB light exposure and offered an accurate and representative measure of S-25(OH)D at the national level. • Unlike most previous studies, the population was first-generation immigrants (foreign-born), and the comparator was native-born Canadians. • The design of the three studies and associated analyses were sufficiently comprehensive to answer the unique research questions. • The findings will contribute to bridging knowledge gaps pertaining to immigrants' health deterioration and vitD deficiency.
Chapter 4.1–4.2 **(CPGs)**	• This systematic review focused on the quality and content of available CPGs that intended to improve the effectiveness and quality of care for immigrants. • The findings will help reduce the knowledge gap by exploring an area that has not been investigated in previous systematic reviews related to this topic.
Chapter 5.1–5.2 **(Global vitD)**	• Unlike previous systematic reviews, the included population was first-generation immigrants (foreign-born), and the comparators were the native-born populations of the host countries. Therefore, all results for first-generation immigrants are considered unique to this systematic review and meta-analysis. • This study followed the WHO recommendation of monitoring migrants' health by collecting and mapping comparable data. • Translating 40 full-text articles from other languages (including 2 studies) made the results globally inclusive. • The study is in progress.
Overall	• The thesis comprehensively covered many pertinent aspects of vitD and immigrants' health. It assessed and integrated different methodological research perspectives and approaches (detailed analyses of national data, a knowledge synthesis by conducting systematic reviews, and guideline evaluation) to establish the key messages from local and universal evidence. This provides policymakers with a better understanding of the national and global immigrants' health problems to help decision-making.

Despite the comprehensive analysis of cross-sectional data and robust methodology of the health technology assessment, there were unavoidable methodological limitations that might have affected the study findings. This section briefly describes these limitations (Table 2).

Table 2. Limitations of the thesis

Chapter/section	Limitations
Chapter 3.1–3.3 **(CHMS data analysis)**	• Immigrants were identified as landed people without detailed information about their immigration-specific status (e.g., if they were refugees or asylum seekers). The lack of data on refugees and asylum seekers limited further subgroup analyses. • The comparator (native-born Canadians) formed a single group, despite some being second- or third-generation immigrants; this resulted in high heterogeneity in the reference population group. • Cross-sectional surveys such as the CHMS are not usually used to examine changes in health over time. The bidirectional association between S-25(OH)D and CDs is complex, and it was challenging to address residual confounding using an observational study design. • CHMS data were used in the analysis as secondary data. This limited the proposed thesis hypothesis and analysis. For example, some of the CDs could not be included in the analysis because the date of diagnosis was not provided.
Chapter 4.1–4.2 **(CPGs)**	• As translating CPGs from other languages was a concern in this study, the included CPGs were limited to those published in English and any full-text CPGs found in other languages were excluded, which might have introduced selection bias. • To answer the section-related research question, the included CPGs were restricted to a 10-year period (2010–2020) to capture the most recent or updated CPGs that most likely used rigorous guideline development criteria, which might have introduced selection bias. However, this method was used as a model for a set of CPGs to assess the quality and content of recent time-limited CPGs.
Chapter 5.1–5.2 **(Global vitD)**	• The secondary objective reported in the protocol was assessing the association between vitD and CDs. However, this could not be implemented in this systematic review because the inclusion criteria were restricted to healthy people and excluded studies among patients. Extant studies showed that those with CDs were more deficient than healthy people, and the baseline S-25(OH)D represented disease-related or supplementation-affected levels. This deviation will be identified as a limitation in the final manuscript. • This study is in progress.
Overall	• The outbreak of Covid-19 and related restrictions caused a massive delay in the original thesis plan. The Research Data Centre shut down for six months and started again but with limited capacity and time. This made access to the data and program files impossible for six months and much slower during the time of the Covid restriction.

6.3 Recommendations and future directions

The results of this thesis will help fill knowledge gaps and support policymaking and program development at the national and international levels. The results also provide direction for further studies. Based on the overall findings of this thesis, the major recommendations are as follows.

Short-term prevention strategies and national intervention programs are needed in both community and clinical settings to improve vitD status, including vitD supplementation, vitD screening programs, and awareness for people at higher risk for vitD deficiency. A long-term intervention plan may include affordable governmental programs, such as vitD-fortified food. Food fortification is considered an effective long-term intervention to combat vitD deficiency or insufficiency. For example, the analysis of CHMS data in this thesis indicated that immigrants consumed more eggs than native-born Canadian, which suggests a program of vitD fortification for eggs may improve S-25(OH)D levels among immigrants. Moreover, national and international CPGs that properly address vitD deficiency among immigrants are needed to reduce global vitD deficiency and health deterioration among immigrants, as well as to bridge gaps between research, policy, and practice. These guidelines should support vitD screening and supplementation for specific vulnerable immigrant population groups (e.g., different ethnicities/origins), and consider culturally appropriate interventions.

Further longitudinal observational research and interventional trials are needed to clarify immigrants' health deterioration and the complicated and controversial bidirectional association between S-25(OH)D and CDs. For example, immigrants could be followed over their residency in their host country to explore the patterns, development, and direction of health deterioration. Moreover, further studies focused on immigrants are recommended to explore genetic variations to address the effect of vitD deficiency on long-term CDs. This may include a comparison of

different generations of immigrants (first- to second- and third-generation) in different regions of the world. This will be necessary to gather evidence and formulate recommendations that are specific to sub-populations or generations that may differ from the overall immigrant population.

6.4 Summary and overall findings

This thesis focused on *two immigrants' global health problems*: health deterioration over time and lower S-25(OH)D. Therefore, immigrants' health deterioration in the context of vitD was investigated at national and international levels.

The comprehensive thesis covered many pertinent aspects related to vitD and immigrants' health. The thesis assessed and integrated different methodological research perspectives and approaches, these were detailed analyses of Canadian national data, a knowledge synthesis by conducting systematic reviews, and guideline evaluation to establish the key messages from local and universal evidence. Assessment of vitD and immigrants' health aspects using different perspectives provides policymakers with a better understanding of the *two immigrants' global health problems* to help decision-making.

Six manuscripts were produced for publication in peer-reviewed journals; five are already published (Sections 3.1, 3.2, 3.3, 4.1, and 5.1), and one has been submitted for publication (Sections 4.2).

In conclusion, the key findings of the thesis are:

- Immigrants' S-25(OH)D levels were lower than non-immigrants at national and international levels. S-25(OH)D levels improved over the years of residency in the host country.
- Ethnicity was the main explanatory factor for variations in S-25(OH)D between the immigrant and non-immigrant groups, suggesting genetic factors may play a role.

- Melanin levels were higher among immigrants (darker-skinned), did not differ by length of stay in Canada, and had a weak positive correlation with S-25(OH)D, suggesting confounding and genetic factors may impact this relationship.
- The longer immigrants lived in Canada, the higher the prevalence of CDs, which may be considered an early sign of health deterioration.
- In addition to the changes in lifestyle and environment, the accumulated lower S-25(OH)D among immigrants may impact their health profile in terms of CD-related biomarkers, partially explaining immigrants' health deterioration over time.
- Current national and international guidance regarding the growing problem of vitD deficiency/insufficiency among immigrants are inadequate.

6.5 Future Work

An additional five related manuscripts are planned for publication. Three publications will be based on the results of Chapter 5, and two will present protocols for national and international CPGs focused on immigrants' health and vitD. The titles of the five manuscripts are as follows:

- Global vitD status among immigrants compared with non-immigrants: systematic review and meta-analysis
- Mapping global vitD levels among first-generation immigrants from different origins compared to native-born population
- Determinants of vitD deficiency among immigrants
- Protocol for a national immigrants' health CPG
- Protocol for an international immigrants' health CPG

6.6 Revision to the thesis based on comments from the thesis examiners (April 20th, 2023)

This section comprises some comments and corrections raised by the examiners during the thesis defence. The CHMS data-related comments were to add a rationale for studying the relationship between melanin (skin pigmentations) and S-25(OH)D. Also, to clarify why the melanin result contradicts the established previous research knowledge of "positive correlations" and "not explaining the variations in S-25(OH)D". Moreover, to enrich the discussion about acculturation and epigenetics, to add to the data limitations "no information about individuals suffering from malabsorption conditions/diseases" (e.g., Celiac, Crohn's), and to clarify more that the finding of

"partial explanations for health deterioration" is not a causal relationship between S-25(OH)D and CDs.

Two more general comments were also raised. The first is to account for modifiable and non-modifiable factors during the analysis. The second is to plan for a logic model for the relationship between risk factors for vitD deficiency and health deterioration among immigrants. The examiners also highlighted minor text editing and corrections for the published manuscripts. The following are, in point-to-point fashion, responses and modifications based on the above-comments.

Rational for studying the relationship between melanin (skin pigmentations) and S-25(OH)D since this relationship was well-established fact from 1982 onward (**Introduction of Chapter 3-section 2).**

Melanin pigment is known to inhibit the photosynthesis of vitD3 because of its function as a biological shield against UV radiation [1-3]. In addition to the inverse association between skin pigmentation and S-25(OH)D, vitD studies found that skin pigmentation is the main explanatory factor for variations in S-25(OH)D [4, 5]. Most importantly, in these previous articles, skin pigmentations were either not reported, self-reported, not accurately measured, observed, or estimated based on ethnicity or immigrants' country of origin as a proxy indicator for skin color. For instance, in a review article for skin pigmentation studies, skin pigmentation was self-reported in 93% of the studies, and only 7% were based on observation or objective measures. Moreover, in a meta-analysis of 36 studies among immigrants from different regions, the authors estimated skin color based on their origins and "region of origin was used as a surrogate measure for skin color." In addition to the negative correlation with S-25(OH)D, the study concluded that skin

pigmentation explains the variation in serum VitD [5]. In a highly cited meta-regression analysis for 394 studies (skin pigmentation estimated for Caucasian with white skin vs. non-Caucasians with darker skin). The conclusion was "Caucasians had on average 21.2±5.1 nmol/l higher serum 25(OH)D levels than non-Caucasians (68±3.2 versus 47±4.0 nmol/l, $p<0.01$, N= 151 studies)" [4]. Furthermore, in addition to the knowledge about melanin synthesis, migration to the skin, and degradation, which is not well established, very few studies evaluated the association between vitD status and objectively measured skin pigmentation [1, 6].

Our study found that melanin is not a major explanatory factor for the variations in S-25(OH)D and is positively correlated with S-25(OH)D [7]. Therefore, to better understand the relationship between melanin and S-25(OH)D, we planned to investigate and address this critical issue of vitD and melanin levels among immigrants from a broad spectrum of ethnicities and origins in this epidemiological study.

Unlike experiments of colorimetric studies, the CHMS data were collected in a cross-sectional design to investigate all vitD-related sociodemographic, environmental, and biological measures, including a reliable measurement for melanin (DSM II ColorMeter method). CHMS national data was used to implement extensive analysis of melanin and vitD for people from different origins/regions/ethnicities for immigrants from five regions, more than 153 countries and more than 13 ethnicities compared to white and or native-born Canadians.

This study will help to understand the mechanisms and the most important factors underlying the relationship between melanin and vitD among people from different origins. Moreover, it wil allow experts in other areas to follow up from clinical and physiological perspectives.

The acculturation and epigenetics aspect (Discussion of Chapter 3-section 3).

The associations between S-25(OH)D and the length of time after immigration may reflect the effects of the environment, lifestyle, and acculturation on immigrants in Canada. Previous immigration studies found that the length of time since immigration was a critical indicator of lifestyle acculturation, and higher acculturation levels were associated significantly with higher S-25(OH)D levels [8, 9]. Our previous study found recent immigrants had less sun exposure and less frequent consumption of vitD-rich foods than previous immigrants, suggesting a reasonable lifestyle adaptation over time in Canada [7].

Epigenetic adaptations may partially explain why previous immigrants living in Western-north countries with lower UVB radiation had better S-25(OH)D levels over time than recent immigrants. Biological adaptation is part of micronutrient gene regulation supporting vitD3 synthesis [1]. Genomic studies showed that vitD interacts and influences the human genome through vitD receptor-mediated gene regulation [1]. Considering that the vitD receptor is expressed in almost every tissue and cell throughout the human body, there are extensive investigations on the potential extra-skeletal effects of vitD [10]. A large-scale data analysis found a difference in S-25(OH)D concentration due to at least six genetic variations across genotypes. These genes were previously shown to have contributed to disease pathologies (e.g., type 2 diabetes mellitus and obesity) [10]. Common genetic polymorphisms in the vitD receptor and vitD-binding protein may partly explain differences in vitD status and health status between different ethnicities [11].

Further studies are needed to explore the possibility of the involvement of genetic variations among different ethnicities to understand better the relationship between vitD deficiency and chronic diseases, including diet-related diseases such as type 2 diabetes mellitus.

Adding CHMS data limitations such as no information about individuals suffering from malabsorption conditions/diseases (e.g., Celiac, Crohn's), (Discussion and limitation of Chapter 3-section 3).

VitD deficiency and insufficiency have been connected to some autoimmune disorders, including Celiac and Crohn's disease[12]. However, none of the autoimmune disorders were part of the CHMS data. Therefore, we did not investigate or account for the effect of these disorders during the analysis due to this limitation.

Clarification about the causal relationship associated with the results of partial explanations for health deterioration (**Discussion of Chapter 3-section 3).**

The inverse associations between S-25(OH)D with CDs-related biomarkers (glycated hemoglobin, total cholesterol/high-density lipoprotein ratio, immunoglobulin E, serum ferritin, and blood hemoglobin) in this study were interpreted as a partial explanation for the health deterioration over time among immigrants in Canada. This interpretation does not represent any causative nature for the association. We recommend further longitudinal research and interventional trials to clarify immigrants' health deterioration and the complicated and controversial bidirectional association between S-25(OH)D and CDs. Moreover, to explore genetic variation studies to address the effect of vitD deficiency on long-term CDs.

Modifiable and non-modifiable factors (Methods and discussions of Chapters 3 and 5).

Risk factors are modifiable and non-modifiable. Modifiable means the risk factors can be changed, and non-modifiable means they cannot be changed. In the CHMS analysis (Chapter 3), the modifiable risk factors were sun exposure, sunscreen use, supplements, dietary intake, smoking, and some health-related modifiable factors like obesity. In contrast, the non-modifiable risk factors

were age, sex, skin color, ethnicity, and origin. Our multivariable analysis did not account for these factors to estimate the mean difference in S-25(OH)D levels. However, we used a systematic approach (backward elimination method) that starts with a complete set of features and removes features (with the least predictive power) one by one until the model performance is optimal. This method is recommended when there is a large set of potential features to be more efficientand and make the model more interpretable. However, in Chapter 5 (global vitD's systematic review), we will implement a sensitivity analysis as part of the meta-analysis to account for vitD deficiency considering modifiable and non-modifiable factors.

Logic model for the relationship between vitD deficiency's risk factors and health deterioration (Methods and discussions of Chapter 5).

Directed Acyclic Graphs and a logic model will be implemented to show the relationship between risk factors to vitD deficiency and CDs (outcomes) considering other important factors such as predisposing (e.g., attitudes), reinforcing (e.g., media and decision-makers) and enabling (e.g. services and policies) factors.

Text corrections to the published papers as follows:

Chapter 3, pages 70, 71, 116, 129, 130, 132, 168, 193.

Original text: serum vitD

Modified text: S-25(OH)D

Chapter 3, page 60.

Original text: (62.72 vs. 51.23 nmol/L, P<0.001).

Modified text: (51.23 vs. 62.72 nmol/L, P<0.001)

Chapter 3, page 70.

Original text: Our multivariate analyses found ethnic background, having traveled to a sunny/warm climate, and low dairy product consumption were strong predictors of low S-25(OH)D levels among immigrants in Canada.

Modified text: Our multivariate analyses found ethnic background, not exposed to a sunny/warm climate two months before vitD's test, and low dairy product consumption were strong predictors of low S-25(OH)D levels among immigrants in Canada.

Chapter 3, page 143.

Original text: The OR increased by 71% among obese participants, by 174% when the HbA1c increased by 1%, and by 0.001% when IgE increased by 1 IU/mL.

Modified text: The OR increased by 92% among obese participants, by 163% when the HbA1c increased by 1%, and by 0.001% when IgE increased by 1 IU/mL.

References

1. McCarty, C.A., Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? The American journal of clinical nutrition, 2008. 87(4): p. 1097S-1101S.
2. Young, A.R., et al., Melanin has a small inhibitory effect on cutaneous vitamin D synthesis: A comparison of extreme phenotypes. Journal of Investigative Dermatology, 2020. 140(7): p. 1418-1426. e1.
3. Pham, T., Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal. Thesis-McGill University, 2012.
4. Hagenau, T., et al., Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporosis international, 2009. 20: p. 133-140.
5. Martin, C.A., U. Gowda, and A.M.N. Renzaho, The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. Nutrition, 2016. 32: p. 21-32.
6. Pham, T., Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal. Thesis-McGill University, 2012.
7. Yousef, S., et al., Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey. Nutrients, 2021. 13(8): p. 2702-2702.
8. Salant, T. and D.S. Lauderdale, Measuring culture: a critical review of acculturation and health in Asian immigrant populations. Social science & medicine, 2003. 57(1): p. 71-90.

9. Sanou, D., et al., Acculturation and nutritional health of immigrants in Canada: a scoping review. Journal of Immigrant and Minority Health, 2014. 16(1): p. 24-34.
10. Zumaraga, M.P., et al., Next generation sequencing of 502 lifestyle and nutrition related genetic polymorphisms reveals independent loci for low serum 25-hydroxyvitamin d levels among adult respondents of the 2013 philippine national nutrition survey. Journal of the ASEAN Federation of Endocrine Societies, 2021. 36(1): p. 56.
11. Leandro, A., et al., Genetic polymorphisms in vitamin D receptor, vitamin D-binding protein, Toll-like receptor 2, nitric oxide synthase 2, and interferon-γ genes and its association with susceptibility to tuberculosis. Brazilian Journal of Medical and Biological Research, 2009. 42: p. 312-322.
12. Tavakkoli, A., et al., Vitamin D status and concomitant autoimmunity in celiac disease. Journal of clinical gastroenterology, 2013. 47(6): p. 515.

Thesis appendices

The following thesis appendices present the PDFs of the five published and one submitted manuscripts, including the PROSPERO registrations in Chapters 3-5 (3.1, 3.2, 3.3, 4.1, 4.2, and 5.1). All the published were in open-access peer review journals. The citation for each PDF, as well as the permissions obtained from the publishers, are provided below:

Appendix A3 (Chapter 3: Section 3.1)

The PDF of the published manuscript is presented in Appendix 3.1

> ***Said Yousef****, Douglas Manuel, Ian Colman, Manny Papadimitropoulos, Alomgir Hossain, MoezAlIslam Faris, and George A. Wells. Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey. Nutrients, 2021. 13(8): p. 2702-2702.*

This manuscript was published under the MDPI License. "Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/)."

Permissions: "No special permission is required to reuse all or part of article published by MDPI, including figures and tables. For articles published under an open access Creative Common CC BY license, any part of the article may be reused without permission provided that the original article is clearly cited. Reuse of an article does not imply endorsement by the authors or MDPI."

Minor change, a typo error in the published version was corrected in the copied manuscript.

Appendix A3 (Chapter 3: Section 3.2)

The PDF of the published manuscript is presented in Appendix 3.2

> ***Said Yousef****, Manny Papadimitropoulos, MoezAlIslam E. Faris, HAYDER A. HASAN, Alomgir Hossain, Ian Colman, Douglas Manuel, George A. Wells. Melanin levels in relation to vitamin D among first-generation immigrants from different ethnic groups and origins: A comparative national Canadian cross-sectional study. Frontiers in Medicine Sec. Dermatology, doi: 10.3389/fmed.2022.992554.*

No changes were made to the published version.

Appendix A3 (Chapter 3: Section 3.3)

The PDF of the published manuscript is presented in Appendix A3.3

> ***Said Yousef****, Ian Colman, Manny Papadimitropoulos, Douglas Manuel, Alomgir Hossain, MoezAlIslam Faris, and George A. Wells. Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data. Nutrients, 2022. 14(9): p. 1760.*

No changes were made to the published version.

Appendix A4 (Chapter 4: Section 4.1)

1- The PDF of the PROSPERO (CRD42021240562) registration Appendix A4.1

***Yousef**, S., L.M. Hayawi, and G.A. Wells, A Systematic Assessment of the Quality and the Content of the Immigrant's Health and Vitamin D's Clinical Practice Guidelines (CPGs) using the AGREE II Instrument, in PROSPERO CRD42021240562. 2021.*

At the outset of a systematic review researchers record key methods on-line. Open access to this information helps other researchers, guideline producers and funders to avoid unintended duplication. Registration in PROSPERO is free and open to anyone undertaking a systematic review of the effects of interventions and strategies to prevent, diagnose, treat, and monitor conditions, for which there is a health-related outcome. Registration increases transparency, avoids unplanned duplication, and helps safeguard against bias. Registration of the systematic review at: www.crd.york.ac.uk/PROSPERO

2- The PDF of the published manuscript (protocol) is presented in Appendix A4.2

> ***Yousef S****, Hayawi L, Manuel M, Colman I, Papadimitropoulos M, Hossain A, Faris M, Wells G. A. Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: A protocol for systematic review. Systematic Reviews, 2022. 11(1): p. 1-5.*

No changes were made to the published version.

Appendix A5 (Chapter 5: Section 5.1)

1- The PDF of the PROSPERO (CRD42018086729) registration Appendix A5.1

> ***Said Abdelrazeq Yousef****, George A. Wells, and Jesse Elliot, Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis, in PROSPERO.* (CRD42018086729) *2018.*

At the outset of a systematic review researchers record key methods on-line. Open access to this information helps other researchers, guideline producers and funders to avoid unintended duplication. Registration in PROSPERO is free and open to anyone undertaking a systematic review of the effects of interventions and strategies to prevent, diagnose, treat, and monitor conditions, for which there is a health-related outcome. Registration increases transparency, avoids unplanned duplication, and helps safeguard against bias. Registration of the systematic review at: www.crd.york.ac.uk/PROSPERO

2- The PDF of the published manuscript (protocol) is presented in Appendix A5.2

> ***Said Yousef****, Jesse Elliott, Douglas Manuel, Ian Colman, Manny Papadimitropoulos, Alomgir Hossain, Nathalie Leclair, and George A. Wells. Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations- a systematic review and meta-analysis. Systematic Reviews, 2019. 8(1): p. 1-6.*

No changes were made to the published version.

nutrients

MDPI

Article

Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey

Said Yousef [1,2,*], Douglas Manuel [3,4,5], Ian Colman [1], Manny Papadimitropoulos [6,7], Alomgir Hossain [1,4], MoezAlIslam Faris [8] and George A. Wells [1,2]

1 School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON K1H 8M5, Canada; icolman@uottawa.ca (I.C.); alhossain@ottawaheart.ca (A.H.); gawells@ottawaheart.ca (G.A.W.)
2 Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON K1Y 4W7, Canada
3 Ottawa Hospital Research Institute, Ottawa, ON K1Y 4E9, Canada; dmanuel@ohri.ca
4 Institute for Clinical Evaluative Sciences, Ottawa, ON K1Y 4E9, Canada
5 Department of Family Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON K1H 8M5, Canada
6 Eli Lilly Canada Inc., Toronto, ON M5X 1B1, Canada; papadimitropoulos_manny@lilly.com
7 Faculty of Pharmacy, University of Toronto, Toronto, ON M5S 3M2, Canada
8 Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah 27272, United Arab Emirates; mfaris@sharjah.ac.ae or moezfaris@hotmail.com
* Correspondence: Said Yousef

Abstract: One in five Canadians are first-generation im migrants. Evidence suggests the baseline risk for vitamin D (vitD) deficiency is increased among immigrants who move from equatorial to northern countries. We investigated the prevalence and determinants of vitD deficiency/insufficiency among first-generation immigrants compared with native-born Canadians and identified explanatory covariables. We used a cross-sectional design with data from the national Canadian Health Measures Survey (Cycles 3 and 4) (11,579 participants aged 3–79 years). We assessed serum 25-hydroxyvitamin D (S-25(OH)D) levels, sociodemographic and environmental factors, immigration status, length of time in Canada, vitD-rich food intake, ethnicity, and place of birth. Immigrants had lower mean S-25(OH)D than non-immigrants (51.23 vs. 62.72 nmol/L, $p < 0.001$). Those with younger age at the time of immigration (<18 years) had a high risk for low vitD, and S-25(OH)D levels increased with the length of time they had lived in Canada. The highest deficiency levels were in immigrants born in Morocco, India, and Lebanon compared with native-born Canadians. Ethnicity was the factor most strongly associated with S-25(OH)D. Compared with the white ethnic grouping, the Japanese had the highest level of vitD deficiency, followed by Arabs and Southeast Asians. Ethnic variations, dietary intake, and lifestyle factors are the main predictors of/explanatory factors for vitD status among Canadian immigrants.

Keywords: vitamin D; serum 25-hydroxyvitamin D; first-generation immigrants; ethnicity; melanin; dietary intake

check for updates

Citation: Yousef, S.; Manuel, D.; Colman, I.; Papadimitropoulos, M.; Hossain, A.; Faris, M.; Wells, G.A. Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey. *Nutrients* **2021**, *13*, 2702. https://doi.org/10.3390/nu13082702

Academic Editors: Anitra Carr and Adrian Gombart

Received: 5 July 2021
Accepted: 3 August 2021
Published: 5 August 2021

1. Introduction

Vitamin D (vitD) plays a crucial role in physiological functions, including skeletal and non-skeletal health [1]. Vit D has two main metabolites, namely 25-hydroxyvitamin D (25-OH) and 1, 25 dihydroxy vitamin D. The dietary sources (vitamin D2 or ergocalciferol) and the animal-based foods (vitamin D3 or cholecalciferol) are the two main forms of vitamin D found in the human body [2–4]. The primary source of vitD in the human body, however, is through skin exposure to sunlight (cutaneous synthesis

of vitD3) [2,5]. Vitamin D2 and D3 are considered to have equal biological value. The total serum 25-hydroxyvitamin D (S-25(OH)D) concentration is the sum of the 25(OH) D2 and 25(OH) D3 concentrations [6]. The concentration of S-25(OH)D represents the combined contributions of the cutaneous synthesis and dietary intake of vitD and is considered the top clinical marker for overall S-25(OH)D level [7–9]. The S-25(OH)D is expressed in nanomoles per liter (nmol/L) and has a stable half-life (up to three weeks) in the human body [7].

The mean of S-25(OH)D (nmol/L) and/or the ranges for the thresholds (a deficiency, <25–30 nmol/L; insufficiency, 25–49 nmol/L; sufficiency, ≥50–<75 nmol/L) were commonly reported and used in studies to describe the status of vitD [8]. The insufficient status (<50 nmol/L) is more frequently used to describe hypovitaminosis D [10]. However, the optimal S-25(OH)D concentration for skeletal health is controversial. The Institute of Medicine (IOM) recommends maintaining S-25(OH)D concentration levels above 50 nmol/L, whereas other experts favor the concentration between 50 to 100 nmol/L [11–13].

Multiple factors affect the body's ability to synthesize vitD, including dietary intake, coexisting disease conditions (especially liver and kidney diseases), and sun-related vitD production (e.g., sun exposure) [8,9,14,15]. Other implicated factors include sociodemographic factors (e.g., socioeconomic status, age, and sex), geographical and environmental factors (e.g., season and latitude), cultural and religious aspects (e.g., clothing and prolonged breastfeeding time), and health and genetic factors (e.g., melanin levels and obesity) [8,10,16]. A global review of evidence from six regions (Europe, North America, Latin America, Asia, the Middle East/Africa, and Oceania) showed the leading risk factors for vitD deficiency were older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, poor dietary habits, and absence of vitD fortification [10].

Hypovitaminosis D is a worldwide public health problem to which immigrants are particularly vulnerable, with a high baseline risk among populations with darker skin who migrate from equatorial regions to northern latitudes [17,18]. Migration is considered a significant risk factor for low S-25(OH)D levels attributable to lifestyle and environmental changes, including dietary intake, physical activity, sun exposure, clothing, and a move from low to high latitude countries [8,17,18]. Immigrants in Canada and other Western countries have a high prevalence of vitD deficiency and insufficiency compared with Western people, with a deficiency prevalence of 19.3–80% among different ethnic minorities [8,15,19]. A meta-analysis of 36 studies reported variation in vitD deficiency among dark-skinned immigrants was attributable to the length of residence in the host country, age at immigration, nutritional barriers, and geographic origins and ethnicities of the studied populations [18]. Moreover, the estimated pooled prevalence of vitD deficiency was 77% (95% confidence interval [CI], 70–83%) after adjustment for latitude [18].

The immigrant population in Canada has increased in recent decades. One in five Canadians is foreign-born, with these people originating from over 200 ethnic groups or origin countries [20]. Research evidence suggests the presence of significant differences in sociocultural contexts and various outcomes between first-generation and second or third generation immigrants [21,22]. Moreover, researchers recommended studying and comparing ethnic groups from the same generation [21–24].

There is a paucity of information about the status of vitD among Canadian immigrants from different ethnic groups and origins. Therefore, we intend to study first-generation immigrants as identified in the Canadian Health Measures Survey (CHMS) data (foreign-born) to investigate vitD status among immigrants compared with the non-immigrant (native-born) population. Most of the previous studies on immigrants' vitamin D involved aggregated generations of immigrants (first, second, or more generations), resulting in high heterogeneity in the study population. Moreover, they focused on specific groups from relatively few ethnicities or few countries of origin. However, this study is the first to report vitD status among large sample of first-generation immigrants from 13 major ethnic

groups and who were migrated from 153 countries of origin compared with white ethnic group and native-born Canadians.

The study aimed to estimate the prevalence and the leading determinants of vitD deficiency/insufficiency among immigrants from different ethnicities and regions/countries of birth compared with white and native-born Canadians. Moreover, to understand the effects of the environment, lifestyle, and acculturation on immigrants' vitD, we aimed to investigate vitD status to the length of time after immigration. We hypothesized that significant differences exist in vitD status between immigrant and non-immigrant Canadians, with immigrants having lower vitD status.

2. Materials and Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was adopted in planning, implementing, and reporting this study [25].

2.1. Study Design and Participants

The CHMS is a cross-sectional population-based survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada [26]. The CHMS provided the first national data on vitD for the Canadian population including immigrants [26]. The CHMS was executed in cycles biannually. Compared to the 2006 Census data and the 2011 National Household Survey, CHMS data has unique information in direct physical health measures, representing the Canadian immigrant population, and addressing the gaps in their existing national information [27].

This study used data for Cycles 3 (2012–2013) and 4 (2014–2015) of CHMS data, which included randomly selected individuals aged 3–79 years [26]. Cycles-3 and -4 were selected as being the most thematic consistent cycles in reporting vitD -rich foods and other vitD determinants than the other cycles of CHMS data. Therefore, we combined Cycles 3 and 4 based on instructions provided by Statistics Canada. By merging the two cycles, we aimed to provide a larger sample size and increase the number of primary sampling units to allow for greater precision in estimating small prevalence and providing more detailed analyses.

For each cycle, Statistics Canada determined the sample size to produce reliable and representative estimates at the national level for sex and age groups. The survey covered approximately 96% of the Canadian population, each cycle collected from sixteen collection sites spread across Canada and stratified into five regions: namely British Columbia, the Prairies (Alberta, Manitoba, and Saskatchewan), Ontario, Quebec, and the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick). A dwelling stratification stage was applied and followed by a roster list of all persons living in the household, and individuals aged 3 to 79 years were randomly selected [26]. All participants provided written informed consent, and the CHMS survey was approved by the Health Canada Research Ethics Board [26].

The CHMS sample population weight was adjusted for age group and sex across Canada's five standard geographic regions [27]. It is worth mentioning that except for the total number of subjects included in the analysis, the number of participants in each group and the unweighted results cannot be published due to Statistics Canada's restrictions policy, thus the results are presented as weighted results. Detailed information about merging the two cycles and the CHMS data are presented in Appendix A and on the Statistics Canada website (http://www.statcan.gc.ca, accessed on 24 February 2021) [28,29].

2.2. Measures

The S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, MN, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. Data for S-25(OH)D in the two cycles were extracted and used as the outcome-dependent factors.

We used four cut-offs for S-25(OH)D to identify vitD status as follows: (<30 (nmol/L); (<50 (nmol/L); (<75 (nmol/L); and (≥75 (nmol/L). First, <30 nmol/L is used to identify

deficient people. Second, (<50 nmol/L) is a cut-off for the insufficient 25(OH) D, which includes the deficient and insufficient people (it is an accumulating value and not range for the insufficient people). Third, (<75 nmol/L) is a cut-off and accumulating value for deficient, insufficient, and sufficient. Fourth (≥75 (nmol/L), is the "no added value" or the "optimal" as defined by IOM or other experts [8,11–13]. The remaining last two cut-offs (<75 nmol/L and ≥75 nmol/L) cover 100% of the total population. We assumed that reporting the prevalence of vitD deficiency, insufficiency, sufficiency, and the no added value or optimal categories using these cut-offs is important for clinicians and readers to see the proportion of participants under each stratified category. Moreover, we used ranges of S-25(OH)D for the above-mentioned cut-offs (<30 nmol/L; 30–49 nmol/L; 50–74 nmol/L and ≥75 nmol/L) for sub-groups of participants.

Independent variables were factors associated with the risk for developing vitD deficiency/insufficiency: immigration status, sex, age, income, education level, body mass index (BMI, kg/m^2), smoking status, alcohol consumption, age at immigration, length of time in Canada, sun exposure, sunscreen use, season and month of blood sampling, clothing type, physical activity, region and country of birth, ethnicity, skin pigmentation (melanin level), intake of vitD-rich foods, and vitD supplements/medications used.

We created BMI norms for adults aged ≥ 18 years according to Health Canada's national standards for weight classification [30]. For children aged 3–17 years, body weight classification was based on World Health Organization percentiles [31]. We used the Canadian Physical Activity Guidelines index to classify participants (aged 5–17 years and ≥18 years) as meeting/not meeting physical activity recommendations [32]. The season of blood sampling was categorized by the month of testing: winter (December–February), spring (March–May), summer (June–August), and fall (September–November). Region of birth was classified using five major regions based on the number of participants: Canada and North America; South/Central America and the Caribbean; Europe; Africa; and Asia. We used Statistics Canada's geographic classifications to identify the country of birth (153 countries; Appendix A), and selected the top 20 countries based on the number of participants (≥30 participants from each) to include in the analysis. These countries were Canada, China, USA, France, Jamaica, UK, Algeria, Mexico, Pakistan, Netherlands, India, the Philippines, Romania, Hong Kong, Germany, Colombia, Morocco, Italy, Iran, and Lebanon. All other countries were grouped into one category (Others). The 153 countries (excluding Canada) were also combined in another category to represent all immigrants. Statistics Canada identifies ethnicity as white and non-white. The non-white group included different major ethnic groups; namely Aboriginal, South Asian, Chinese, Black, Filipino, Latin American, Arab, Southeast Asian, West Asian, Korean, Japanese, multiple ethnicities, and others. As reported by Statistics Canada, melanin levels were used as an indicator for skin pigmentation, with higher ranks indicating darker skin.

The steps used to combine the two cycles and to calculate the variables of interest are described in Table A1, Appendix A.

2.3. Statistical Analyses

We summarized the data using numerical and graphical descriptive statistics. All statistical comparisons used the mean (standard error, SE) for continuous variables and proportions with 95% CIs for categorical variables. Data were stratified for analysis based on the variables of interest. To account for the unequal probability of selection and represent an accurate estimate of the Canadian population, we used the survey command, recommended sample weight, and degrees of freedom in the analyses. All results were weighted values. We used continuous values for S-25(OH)D in the linear regression models. A univariate analysis was used to identify independent covariates. Multivariable analyses were performed to clarify the relationship between S-25(OH)D and immigration status and highlight the factors most strongly associated with lower concentration levels of S-25(OH)D among immigrants.

We used the backward elimination method in a linear regression model adjusted for several independent covariates; namely age, sex, household income, education, BMI, season, sun exposure, sunscreen, country of birth, melanin levels, ethnicity, vitD medication and supplements, and food consumption variables. In our analysis, we applied several evaluation models. In which we determined, by excluding variables with a high percentage of missing data (e.g., margarine consumption) and variables that are influenced by S-25(OH)D levels (e.g., serum calcium), improvements in the model's estimation which better represents the study population compared to other models. Statistical significance was set at $p \leq 0.05$. Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Stata version 16.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Study Description and Participants Characteristics

The analyses were based on the total number of participants in both cycles. The combined response rate at the Canadian level (response rate for all study components like the household visit, blood samples, and activity monitor) for Cycle-3 was 51.7%, and Cycle-4 was 53.7% [33,34]. Demographic characteristics for the two cycles are presented in Table A2, Appendix B.

There were 11,579 participants (5785 from Cycle-3 and 5794 from Cycle-4) aged 3–79 years, with a mean (standard error [SE]) age of 39.23 (0.085) years. S-25(OH)D levels were available for 11,009 participants and were normally distributed with an overall weighted mean of 60.28 nmol/L. Nearly 10.30% of Canadians were vitD deficient, 63.64% had insufficient vitD, 76.1% had sufficient vitD, and 23.90% had optimal vitD status.

Table 1 presents the main characteristics of immigrant and non-immigrant Canadians. Immigrants represented 21.9% of the Canadian population (about 53% female), and the majority were of non-white ethnicity. Compared with the non-immigrant population, they were older (overrepresented in the group aged $\geq$ 18 years) and had lower household income, smoking, alcohol consumption, BMI (obesity), sun exposure during peak time, and sunscreen use. However, immigrants were more likely to have higher education levels, wear concealing clothing, and have traveled to sunny/warm climates in the two months before blood sampling than non-immigrants.

The weighted mean melanin level (index values) was higher among immigrants than non-immigrants (17.08 vs. 16.29, $p = 0.004$). Immigrants also had lower household income, and serum calcium and phosphorus levels than non-immigrants. Despite the high statistical difference of calcium ($p = 0.004$) and phosphorus ($p = 0.006$), the biological significance of the mean differences between immigrants and non-immigrants for calcium (2.40 vs. 2.42, respectively) and phosphorus (1.32 vs. 1.36, respectively) were negligible (Table 1). Non-immigrants reported more frequent consumption of vitD-rich foods (red/processed meats, liver, milk, cheese, dairy products, fortified margarine, and fatty fish) (Table A3, Appendix B).

3.2. S-25(OH)D Concentration and VitD Status by Sociodemographic, Lifestyle, and Immigration Features

Table 2 shows the weighted mean S-25(OH)D levels and vitD status by sociodemographic and lifestyle factors. Youth aged 12–17 years had the lowest S-25(OH)D levels. There were significant differences in sex, BMI (obesity), vitD supplement/medication use, sunscreen use, sun exposure during peak time (<30 min/day) and traveling to a sunny/warm climate in the two months before blood sampling. Differences were also found in income, smoking, alcohol consumption, physical activity, and clothing type as shown in Table A3 (Appendix B).

Immigrants had lower mean S-25(OH)D levels than non-immigrants (62.72 vs. 51.23 nmol/L, $p < 0.001$). Age at immigration was associated with 25(OH)D levels; younger generations (<18 years) had a higher risk for lower vitD than older people ($\geq$18 years). Moreover, years of residency after immigration was associated with S-25(OH)D levels, especially at 5 and 10 years, indicating that immigrants had higher S-25(OH)D levels the

longer they had lived in Canada. The mean S-25(OH)D level was higher among sunscreen users than non-users (62.86 vs. 54.78 nmol/L, $p < 0.001$).

Nearly 64% of participants had insufficient S-25(OH)D levels. VitD deficiency was twice as common among immigrants as non-immigrants. Moreover, compared with non-immigrants, more immigrants had insufficient vitD (52.82% vs. 31.75%) and fewer had optimal vitD (13.89% vs. 26.83%; $p < 0.001$). The more years immigrants had lived in Canada, the greater the proportion with optimal levels at 5 (15.41% vs. 7.65%, $p = 0.002$) and 10 (17.37% vs. 7.95%, $p = 0.022$) years after immigration (Table 2). The S-25(OH)D and vitD status by household income, education, smoking habits, alcohol consumption, physical activity, pregnancy, and clothing type are presented in Table A4, Appendix B.

Table 1. Weighted prevalence of immigrants and non-immigrants by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures Survey data.

		Non-Immigrants (78.9%), %	**Immigrants (21.9%), %**	**All Participants (100%), %**	***p*-Value**
Sex	Female	49.37	52.85	50.13	0.142
Age (years)	<5	2.84	0.42	2.31	<0.001
	5–11	9.37	3.38	8.05	
	12–17	8.20	4.57	7.41	
	18–64	69.10	75.41	70.48	
	>64	10.49	16.22	11.75	
Household income (CAD)	<50,000	33.15	43.93	35.51	0.008
	50,000–100,000	37.07	34.65	36.54	
	>100,000	29.79	21.43	27.95	
Education	>Secondary school	47.26	64.63	51.07	<0.001
BMI (kg/m^2)	Underweight	2.19	2.34	2.22	0.023
	Normal weight	41.40	41.75	41.48	
	Overweight	30.21	37.01	31.70	
	Obese	26.21	18.89	24.60	
Ethnic group	Non-white	11.76	62.67	22.91	<0.001
VitD-supplement and/or analog use	Yes	5.39	4.84	5.27	0.664
Smoking status	Current smoker	22.65	14.75	20.79	0.003
Alcohol	Current drinker	82.90	65.03	78.69	<0.001
Meet the physical activity recommendations	Yes	35.41	30.17	34.21	0.127
Sun exposure (10 am to 4 pm)	≥30 min/day	91.21	78.59	88.46	<0.001
Sunscreen use	Yes	73.94	58.57	70.64	<0.001
Clothing	Typically covered	34.66	52.54	38.51	<0.001
Traveled to sunny/warm climate	Yes	10.56	16.48	11.85	0.018
Weighted means		Mean (SE)	Mean (SE)	(95% CI)	*p*-value
	Age (years)	37.51 (0.26)	45.17 (0.58)	(−9.05, −6.26)	<0.001
	Income (CAD)	91,985 (3831)	76,317 (4004)	(8087, 23,248)	<0.001
	Calcium (mmol/L)	2.42 (0.00)	2.40 (0.01)	(0.01, 0.04)	0.004
	Phosphorus (mmol/L)	1.36 (0.01)	1.32 (0.01)	(0.01, 0.06)	0.006
	Melanin (index values)	16.29 (0.29)	17.08 (0.25)	(−1.29, −0.28)	0.004

BMI, body mass index; CAD, Canadian dollars; SE, standard error; CI, confidence interval. *p*-value: $p \leq 0.05$.

Table 2. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D Status			
		Mean (SE)	**(95% CI)**	***p*-Value**	**<30 (nmol/L (10.3%),%**	**<50 (nmol/L (63.64%),%**	**<75 (nmol/L (76.1%),%**	**≥75 (nmol/L (23.9%),%**
Immigration status	Non-immigrant †	62.72 (1.73)	-		7.82	31.75	73.21	26.83
	Immigrant	51.23 (1.41)	(8.37, 14.62)	<0.001	19.01 ***	52.82 ***	86.11	13.89 ***
Age at immigration (years)	<18 †	46.54 (1.63)	-		19.17	64.04	91.37	8.63
	≥18	56.33 (2.34)	(−15.14, −4.44)	0.001	18.80	41.23 **	80.76	19.24 **
5 years after immigration	≤5 †	45.94 (2.22)	-		19.55	62.54	92.35	7.65
	>5	52.77 (1.73)	(−12.58, −1.08)	0.022	18.59	50.04 *	84.59	15.41 *
10 years after immigration	≤10 †	47.03 (1.83)	-		19.55	59.83	92.05	7.95
	>10	53.98 (1.83)	(−11.79, −2.12)	0.007	18.59	48.26	82.63	17.37 **
Sex	Male †	57.92 (1.67)	-		11.13	39.65	79.62	20.38
	Female	62.53 (1.82)	(−6.30, −2.93)	<0.001	9.45	33.04 ***	72.58	27.42 ***
Age group (years)	<5	69.94 (1.64)	(−13.94, −9.01)	<0.001	1.99	15.70	67.1	32.9
	5–11	62.49 (2.16)	(−5.91, −2.29)	<0.001	4.04	27.41	77.9	22.1
	12–17	55.76 (1.93)	(0.44, 4.81)	0.021	10.49	40.38	84.36	15.64
	18–64 †	58.45 (1.81)	-		12.1	39.79	78.24	21.76
	>64	71.07 (1.20)	(−15.63, −9.55)	<0.001	4.59	22.39 ***	58.69	41.31 ***
BMI (kg/m^2)	Underweight	62.19 (4.05)	(−5.82, 7.51)	0.795	12.65	33.0	71.07	28.93
	Normal weight †	63.03 (2.04)	-		9.22	31.79	73.07	26.93
	Overweight	61.02 (1.68)	(−0.56, 4.58)	0.119	7.91	35.32	75.24	24.76
	Obese	54.48 (1.74)	(5.50, 11.60)	<0.001	15.25 ***	45.15 ***	82.36	17.64 **

Table 2. *Cont.*

		S-25(OH)D (nmol/L)			S-25(OH)D Status			
		Mean (SE)	**(95% CI)**	***p*-Value**	**<30 (nmol/L (10.3%),%**	**<50 (nmol/L (63.64%),%**	**<75 (nmol/L (76.1%),%**	**≥75 (nmol/L (23.9%),%**
VitD-supplement and/or analog use	No †	56.97 (1.74)	-		40.52		80.56	19.44
	Yes	83.46 (5.25)	(−35.92, −17.06)	<0.001	9.80 ***		43.16	56.84 ***
Sun exposure (10 am to 4 pm)	<30 min/day †	55.92 (2.20)	-		15.58	48.72	76.51	23.49
	≥30 min/day	60.82 (1.69)	(−7.81, −1.99)	0.002	9.60 **	34.65 ***	76.04	23.96
Sunscreen use	Never †	54.78 (1.85)	-		15.04	48.05	80.92	19.08
	Always, occasionally	62.86 (1.74)	(−10.16, −5.99)	<0.001	7.87 ***	30.23 ***	73.99	26.01 ***
Traveled to sunny/warm climate	No †	59.33 (1.83)	-		10.81	37.99	77.59	22.41
	Yes	67.03 (2.10)	(−11.85, −3.54)	0.001	6.49	23.71 ***	65.08	34.92 ***

Note: Following the Statistics Canada guideline, some cells merged due to the low number of participants. † Reference value; SE, standard error; CI, confidence interval; BMI, body mass index. *p*-values: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

3.3. S-25(OH)D Concentration and VitD Status by Participants' Ethnicity and Country of Origin

Differences were observed in mean S-25(OH)D levels between all ethnic groups compared with the white grouping (mean 64.48 nmol/L), except for the West Asian and Korean groups (Table 3). The lowest mean was reported for the Japanese (33.16 nmol/L; $p < 0.001$), followed by Arabs (37.14 nmol/L; $p < 0.001$), and Southeast Asians (40.92 nmol/L; $p < 0.001$). Compared with the white grouping (6.61%), more than half (55%) of the Japanese ethnic group had vitD deficiency, with similar proportions found for Arabs (52%) and Southeast Asians (41.1%). Moreover, the Japanese had the highest insufficiency level (85%), followed by Koreans (81.0%), and Southeast Asians (73.8%). The ranges for insufficiency (30–49 nmol/L) and sufficiency (50–74 nmol/L) for each ethnic group are also presented in Figure A1, Appendix B.

Table 4 highlights the marked differences among those born in Africa, Asia, and South/Central America, and Caribbean regions. The highest rates of deficient and insufficient vitD were found among immigrants from Africa (31.2% and 68.6%, respectively) and Asia (24.5% and 69.7%, respectively) compared with those born in Canada and North America (7.7% and 31%, respectively). The ranges for insufficiency (30–49 nmol/L) and sufficiency (50–74 nmol/L) for the above mentioned five regions are presented in Figure A2, Appendix B.

Table 3. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by ethnicity using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D Status			
		Mean (SE)	**(95% CI)**	***p*-Value**	**<30 (nmol/L (10.3%),%**	**<50 (nmol/L (63.64%),%**	**<75 (nmol/L (76.1%),%**	**≥75 (nmol/L (23.9%),%**
White †		64.48 (1.73)	-		6.61	29.10	71.25	28.75
Non-white		47.67 (1.31)	(13.85, 19.77)	<0.001	21.09 ***	60.49 ***	90.39	9.61 ***
	Aboriginal	55.55 (1.77)	(4.36, 13.50)	0.001	10.63	40.35 **	82.51	17.49 *
	South Asian	45.56 (2.48)	(13.83, 24.02)	<0.001	22.11 ***	66.73 ***	91.28	8.72 ***
	Chinese	46.03 (1.56)	(14.17, 22.74)	<0.001	17.18 ***	61.84 ***	94.89	5.11 ***
	Black	43.82 (2.96)	(15.07, 26.26)	<0.001	28.87 ***	67.72 ***	91.73	8.27 ***
	Filipino	49.39 (3.93)	(5.90, 24.29)	0.003	7.51	58.85 *	90.41	9.59 ***
	Latin American	52.64 (2.87)	(5.20, 18.50)	0.001	13.43	38.66	92.13	7.87 *
	Arab	37.14 (4.62)	(18.15, 36.54)	<0.001	51.98 ***	72.17 ***	94.40	5.60 ***
	Southeast Asian	40.92 (4.43)	(13.88, 33.24)	<0.001	41.08 ***	73.84 ***	91.19	8.81 **
	West Asian	53.74 (6.64)	(−3.29, 24.78)	0.127	13.83	58.27 **	83.35	16.65
	Korean	44.26 (15.06)	(−10.07, 50.51)	0.180	25.12 *	81.04 ***	18.96	
	Japanese	33.16 (8.59)	(14.12, 48.52)	0.001	55.30 ***	86.27 ***	13.83	
	Multiple ethnicities	53.04 (2.44)	(6.45, 16.44)	<0.001	14.48 **	46.58 ***	88.83	11.17 ***
	Other ethnicities	50.02 (5.17)	(3.33, 25.61)	0.013	62.13 ***	88.36	11.64	62.13 ***

Note: following the Statistics Canada guideline, some cells merged due to the low number of participants. † Reference value; SE, standard error; CI, confidence interval. *p*-values: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

The highest mean S-25(OH)D level was found in those born in the Netherlands, followed by the UK and Germany (72.7, 68.9, and 68.5 nmol/L, respectively). The lowest mean levels of S-25(OH)D were found in those from Algeria (34.7 nmol/L, $p < 0.001$), Lebanon (39.4 nmol/L, $p = 0.008$), and Morocco (39.4 nmol/L, $p = 0.003$). The highest deficient levels were found in those from Morocco (55.9%), India (34.4%), and Lebanon (about 30%), with the highest insufficient levels in those from Algeria (87.9%), Romania

(80.7%), and Lebanon (78.7%). The ranges for insufficiency (30–49 nmol/L) and sufficiency (50–74 nmol/L) for each birth country are presented in Figure A3, Appendix B.

Table 4. Weighted mean S-25(OH)D (nmol/L) and vitamin D status by geographical region and country of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D Status			
		Mean (SE)	**(95% CI)**	***p*-Value**	**<30 (nmol/L (10.3%),%**	**<50 (nmol/L (63.64%),%**	**<75 (nmol/L (76.1%),%**	**≥75 (nmol/L (23.9%),%**
Region of birth	Canada and North America †	63.10 (1.74)	-	-	7.66	30.95	72.74	27.26
	South/Central America, and the Caribbean	53.20 (3.13)	(2.47, 17.33)	0.011	14.65	43.29	86.51	13.49
	Europe	62.61 (1.83)	(−2.98, 3.95)	0.775	8.62	31.24	77.46	22.54
	Africa	42.74 (3.50)	(13.08, 27.64)	<0.001	31.16 ***	68.55 ***	90.21	9.79 **
	Asia	43.67 (1.67)	(15.51, 23.34)	<0.001	24.50 ***	69.67 ***	93.41	6.59 ***
Country of birth	Canada †	63.23 (1.74)	-		7.45	30.73	72.64	27.36
	China	48.62 (2.08)	(10.21, 19.01)	<0.001	10.53	63.14 ***	91.50	8.50 ***
	USA	58.67 (4.07)	(−4.36, 13.47)	0.301	15.44 *	39.01	75.69	24.31
	France	56.98 (5.19)	(−4.17, 16.67)	0.226	34.10		90.52	9.48
	Jamaica	51.72 (7.47)	(−5.03, 28.05)	0.163	23.13 *	48.04	77.07	22.93
	UK	68.88 (3.16)	(−12.11, 0.81)	0.083	11.73	21.95	66.34	33.66
	Algeria	34.73 (6.35)	(15.49, 41.50)	<0.001	87.90 ***		12.10	
	Mexico	45.67 (11.69)	(−5.28, 40.40)	0.125	56.61		87.81	12.19
	Pakistan	41.60 (7.35)	(4.35, 38.90)	0.017	25.96 *	68.38	31.60	
	Netherlands	72.69 (5.75)	(−20.12, 1.20)	0.079	20.06		45.01	54.99 ***
	India	42.40 (4.69)	(11.64, 30.02)	<0.001	34.42 ***	73.64	93.64	6.36 ***
	Philippine	48.14 (3.55)	(7.25, 22.92)	0.001	11.20	61.20 *	91.32	8.68 **
	Romania	42.95 (5.25)	(9.26, 31.29)	0.001	80.72 ***		19.30	
	Hong Kong	53.90 (7.90)	(−8.08, 26.74)	0.278	32.02		68.00	
	Germany	68.53 (6.84)	(−19.37, 8.77)	0.443	29.44		70.19	29.81
	Colombia	60.53 (9.88)	(−19.08, 24.48)	0.800	9.39		77.36	22.64
	Morocco	39.39 (7.25)	(8.77, 38.90)	0.003	55.90 ***	68.53 ***	31.50	
	Italy	63.12 (5.43)	(−10.52, 10.73)	0.984	8.07	24.55	72.49	27.51
	Iran	49.99 (6.87)	(−1.77, 28.23)	0.081	6.18	73.32 **	87.94	12.06
	Lebanon	39.38 (8.18)	(6.89, 40.80)	0.008	29.97 **	78.70 **	21.30	
	Others	49.28 (1.57)	(10.58, 17.31)	<0.001	21.97 ***	54.45 ***	90.19	9.8%
	All (153 Countries)	51.09 (1.40)	(9.01, 15.27)	<0.001	18.91 ***	53.42 ***	86.66	13.34 ***

Note: following the Statistics Canada guideline, some cells merged due to the low number of participants. † Reference value; SE, standard error; CI, confidence interval. *p*-values: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

3.4. S-25(OH)D Concentration and VitD Status by Immigration Status and Season

The S-25(OH)D increased substantially during summer and fall compared with winter. Compared with January, the lowest weighted mean was found in February and the highest in September. The highest percentage of change (−37%) from the optimal level (75 nmol/L) was in February (Figure 1) and (Table A5, Appendix B). Non-immigrants had higher S-25(OH)D in all seasons, with significant increments in spring, summer, and fall compared with the winter season (Figure 2) and (Table A6, Appendix B).

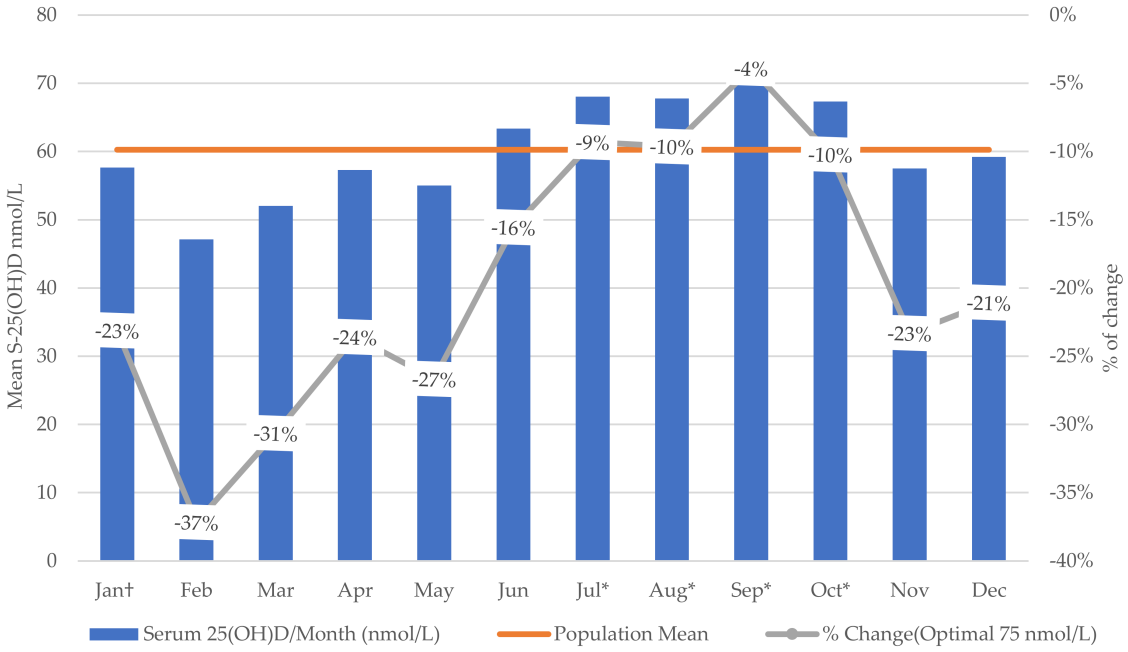


Figure 1. Weighted mean S-25(OH)D (nmol/L)/month of test and percentage of change from the optimal level (75 nmol/L) using Cycles 3 and 4 of Canadian Health Measures Survey data († reference value * significant at $p \leq 0.05$).

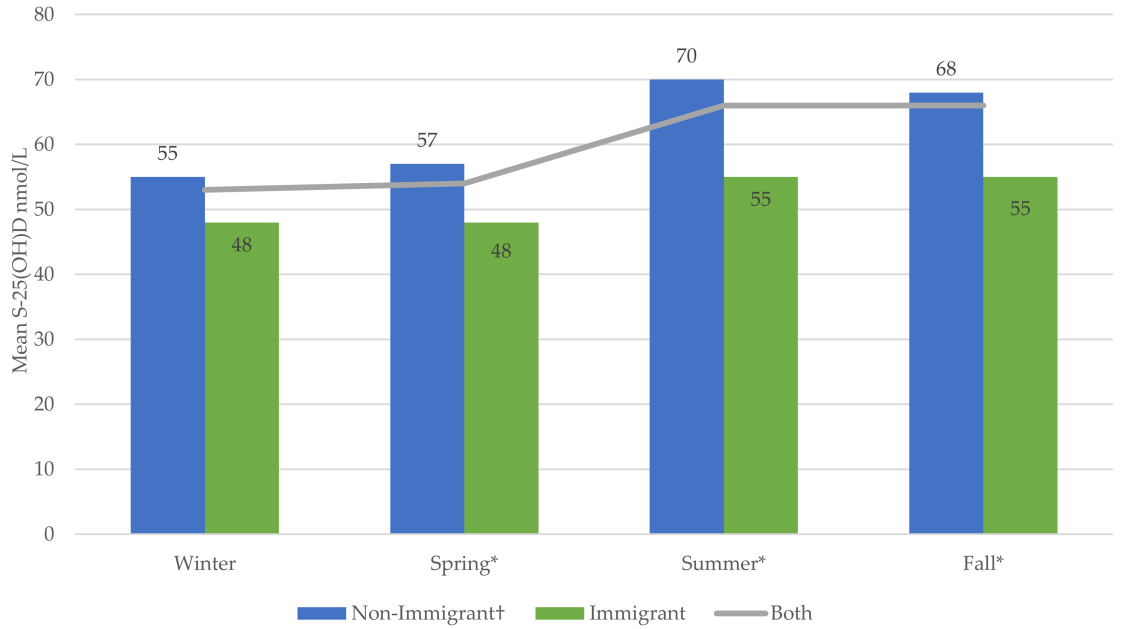


Figure 2. Weighted seasonal variation in mean S-25(OH)D (nmol/L) based on immigration status using Cycles 3 and 4 of Canadian Health Measures Survey data († reference value * significant at $p \leq 0.05$).

3.5. Results of Multivariate Analysis

The final multi-linear regression model showed that immigrants had lower S-25(OH)D levels compared with non-immigrants (beta-estimate: −5.28, 95% CI: −7.48, −3.09, $p < 0.001$) after adjusting for all covariates (Table 5). Ethnicity was the strongest predictor of S-25(OH)D in immigrants compared with non-immigrants. Other predictors such as consumption of dairy products (milk, cheese, and yogurt) and traveling to a sunny/warm climate in the two months before blood sampling were also strongly associated with differences in S-25(OH)D. Overall, the model showed a robust association between immigration status and concentrations of S-25(OH)D.

Table 5. Multivariate analysis-backward elimination method based on S-25(OH)D (nmol/L) and immigration status using Cycles 3 and 4 of Canadian Health Measures Survey data.

	S-25(OH)D		
	Beta Estimate (SE)	**(95% CI)**	***p*-Value**
Immigration status	−5.28 (1.06)	−7.48, −3.09	<0.001
Sex	4.54 (0.88)	2.71, 6.36	<0.001
Season	3.44 (0.97)	1.42, 5.46	0.002
Age	0.14 (0.04)	0.07, 0.22	0.001
Traveled to a warm/sunny climate	6.31 (1.67)	2.85, 9.78	0.001
BMI	−4.89 (0.64)	−6.11, −3.48	<0.001
Dairy products (milk, cheese, yogurt)	5.79 (0.74)	4.25, 7.32	<0.001
Skin pigmentation (melanin)	1.36 (0.28)	0.79, 1.93	<0.001
Sunscreen use	4.95 (1.12)	2.63, 7.28	<0.001
Ethnicity	−15.11 (1.61)	−18.46, −11.78	<0.001
VitD-supplement and/or analog use	0.52 (0.16)	0.17, 0.86	0.005
-Const.	29.01 (5.91)	17.91, 40.12	<0.001

Adjusted linear regression for age, sex, income, education, BMI, season, sun exposure, sunscreen use, country of birth, melanin levels, ethnicity, vitD-medication/supplements, and food consumption variables. Significant at $p \leq 0.05$. BMI, body mass index; SE, standard error; CI, confidence interval.

4. Discussion

This is the first national Canadian study to report vitD status among immigrants from different ethnic groups and origins compared with non-immigrants and has a global impact. A previous systematic review noted the need to assess vitD status and its determinants (including lifestyle factors) among subgroups living in the same country [35]. Moreover, research has highlighted the importance of comparing the same generation of immigrants rather than an aggregated generation [22], and gathering evidence, and formulating recommendations specific to sub-populations that may differ from the overall immigrant population [16].

The higher overall prevalence of vitD insufficiency among immigrants than non-immigrants in this study was consistent with global evidence suggesting that immigrants in Western countries have lower S-25(OH)D levels than non-immigrant populations [8,10,36,37]. Our multivariate analyses found ethnic background, having traveled to a sunny/warm climate, and low dairy product consumption were strong predictors of low S-25(OH)D levels among immigrants in Canada. Consistent with our findings, associations between S-25(OH)D levels and low income, winter season, low sunlight exposure, conservative dress, BMI (obesity), vitD supplements use, low physical activity, less traveling to a sunny/warm climate, non-white ethnicity, place of birth, and skin pigmentation were reported in previous studies [1,10,18].

While females are usually at higher risk for vitD deficiency [8,36–38], females in our study had markedly higher serum S-25(OH)D levels than males. In 2015, Statistics Canada reported that females had more elevated serum of vitD than males, more frequently using supplements than males (41% vs. 28%, respectively), and nearly 85% of vitD supplement users were above the cut-off (<50 nmol/L) compared with non-users (59%) [15]. McCormack et al. 2017, reported that females ≥ 19 years in Canada were using nutritional supplements (including vitD) more than males [39]. However, the higher levels of S-25(OH)D could be partly explained by the finding that females used vitD supplements more than males (66% vs. 34%, $p = 0.019$) (data not shown). In compliance with our finding, studies demonstrated that women who wear concealing clothes had lower S-25(OH)D levels than women dressed according to Western-style. It was well documented that the type of clothing determines the degree of sun exposure and supports/eliminates vitD's epidermal synthesis [8,10,18,40,41]. In this study, the effect of dress style on S-25(OH)D levels reduced (95% CI: −0.67 15.82; $p = 0.070$) in winter when both immigrants and non-immigrants wear winter clothes that cover all the body, while the difference remained statistically significant for spring, summer, and fall which may be due to different type of clothing during these seasons.

The current study found that immigrants with low household income were more linked with lower S-25(OH)D levels. A global vitD review reported that higher family income in developing countries was found inversely associated with hypovitaminosis D [10]. Other studies confirmed that lower-income immigrants were found with lower levels of S-25(OH)D than higher incomes [42,43]. Consistent with our findings, global and Canadian vitD studies reported that obese adults had significantly lower S-25(OH)D than normal/underweight and overweight [1,8,15,44]. Studies suggested that this may be due to vitD displacement in adipose tissue, which results in lower circulating S-25(OH)D levels in the blood [8].

Dairy products contain essential nutrients including vitD and calcium. Previous studies suggested insufficient consumption of these products was strongly associated with lower S-25(OH)D levels [10,42,45,46]. Furthermore, milk in Canada is fortified with vitD, indicating a possibly magnified contribution of dairy products to serum vitD for both immigrant and non-immigrant consumers. Nonetheless, consumption of fortified milk and dairy products was relatively higher in non-immigrants than immigrants, which may partially explain the difference in S-25(OH)D levels.

Canada regions have different weather conditions; nonetheless, it is expected that days in fall and winter are shorter than in summer and spring, with fewer hours of sunlight overall in Canada. In the present study, immigrants had less sun exposure than non-immigrants and had lower S-25(OH)D levels in winter than in summer. The seasonal variation in S-25(OH)D between immigrants and non-immigrants may be explained by the role of ultraviolet-B (UVB) light exposure in the endogenous synthesis of vitD. Previous studies also reported seasonal variations in vitD status [10,19,47]. Other studies reported the lowest levels of S-25(OH)D in winter [8,48], which was consistent with our findings.

The non-sunscreen users had a higher prevalence of deficiency and insufficiency in vitD status than did the frequent sunscreen users. However, such difference could be partly explained by the fact that sunscreens are used as photoprotector as it minimizes ultraviolet-B (UVB) light exposure, hence lowers endogenous vitD activation, and thus increases the likelihood of developing vitD deficiency [49]. Nonetheless, in practice, sometimes the irregular use of sunscreen or inadequate amounts may not be enough to secure the body from all UVB light. Furthermore, sunscreen users might feel sunburn protected by blocking UVB light and, hence, tend to expose themselves more to the sun than non-users, increasing S-25(OH)D levels. In line with our finding, 25% of studies in a recent review concluded that sunscreen use was associated with higher S-25(OH)D concentration, while 10% of studies reported lower levels and 35% with no association [49,50]).

Our data were obtained from immigrants from more than 150 countries, over 13 major ethnic groups, and therefore present a unique contribution to understanding Canada's ethnocultural diversity concerning vitD status. Irrespective of the length of time living in Canada, immigrants who were born in Africa and Asia had lower S-25(OH)D levels than those born in North America. The lowest levels by country of birth were among immigrants born in Algeria, Lebanon, and Morocco. In terms of ethnic origins, the lowest S-25(OH)D levels were in Japanese, followed by Arab and Southeast Asian ethnic groups. Our adjusted linear regression model indicated ethnicity was the most important indicator of low S-25(OH)D levels among immigrants compared with non-immigrants. Similarly, previous research reported vitD deficiency was more common in people from specific racial backgrounds. For example, Asian (South Asia, Southeast), African, and Middle Eastern immigrant populations had lower S-25(OH)D than their counterparts in Western countries [8,10,48]. Middle Eastern immigrants (including Lebanese and Iranian people) were more frequently reported to have deficient/insufficient levels than other ethnic groups and non-immigrant populations in Western countries [10]. A systematic review of 112 studies (168,389 participants from 44 countries) reported insufficient levels in one-third of the included studies, with the highest levels among participants living in North America and lower levels among those living in the Middle East and African regions [35].

Dark-skinned individuals have a rich amount of melanin, which acts as a biological shield against UV radiation [8]. In the present study, skin pigmentation was used to rank

participants based on melanin index values, where higher degrees of melanin indicated darker skin pigmentation. We found that immigrants had higher melanin levels than non-immigrants. Brook et al. reported the median 25(OH)D concentrations were higher in whites compared with non-whites in Canada [51] and several other studies have documented associations between skin pigmentation, ethnicity, geographical origins, and S-25(OH)D levels [8,18,52]. Research suggests that dark-skinned immigrants are at higher risk for vitD deficiency the longer time they spend in the host country [18]. In contrast, we found immigrants had markedly higher S-25(OH)D levels the longer they had lived in Canada after immigration. However, integration into a new life in Canada may reflect physical and behavioral adaptation to the surrounding environment, including lifestyle, diet, and climate changes. Immigration studies on acculturation and vitD found the length of time since immigration was a crucial indicator of lifestyle acculturation, and higher acculturation levels were associated with significantly higher S-25(OH)D levels [21,53]. However, we found immigrants had less sun exposure and less frequent consumption of vitD-rich foods than non-immigrants, and the length of time since immigration reflected reasonable lifestyle acculturation in Canada. Moreover, genomic studies showed that vitD interacts and influences the human genome through vitD receptor-mediated gene regulation and drives evolution for genomic adaptations in the context of skin color lightening [54]. The biological adaptation process is part of micronutrient gene-regulation that supports vitD3 synthesis in regions with lower UVB radiation [54]. Therefore, epigenetic adaptations may partially explain why immigrants in Canada were prone to vitD deficiency in the short term after immigration, and levels of S-25(OH)D increased over time. Furthermore, our study showed that ethnic differences played a fundamental role in S-25(OH)D levels. Common genetic polymorphisms in the vitD receptor and vitD-binding protein may partly explain differences in vitD status between different ethnicities [55]. Therefore, vitD insufficiency and deficiency among immigrants may be associated with genetic variations combined with dietary and other environmental factors; this issue warrants further investigation.

To our knowledge, this was the first study assessing S-25(OH)D levels among Canadian immigrants' different ethnic groups and origins compared with the non-immigrant population at the national level. The findings highlighted the need for further research investigating immigrants' health deterioration in the context of vitD. In addition, building knowledge of the relationship between health deterioration and vitD status along with similar biomarkers has important implications for responding to chronic and infectious diseases, including COVID-19.

Our study should be interpreted with consideration of its strengths and limitations. The CHMS data have many strengths. First, the CHMS provided the first national, comprehensive, and representative data for the Canadian population on vitD. Moreover, it used several clinical and laboratory measures to overcome the limitations of self-reported data [27]. Second, the study design and large sample size provided a nationally representative sample of immigrants in Canada. Third, it captured the ethnocultural diversity of immigrants from more than 150 countries and represented more than 13 major ethnic groups. Fourth, reported melanin level is a reliable indication of skin pigmentation. Fifth, S-25(OH)D levels were collected over the entire year, which enabled adjustment for seasonal variations in UVB light exposure, and offered a more accurate and representative measure of S-25(OH)D at the national level. Finally, the data were validated against other national data such as the Canadian Community Health Survey, Census data, and the 2011 National Household Survey [27]. However, immigrants were identified as landed people without detailed information about the immigration-specific status (e.g., refugees or asylum seekers) [27]. Research suggests refugees have a higher risk for vitD deficiency than other population groups [18,19,56,57]. The lack of data on refugees and asylum seekers limited further subgroup analyses. Another limitation of CHMS data is that the levels of biologically activated form 1,25(OH)2Dwas not measured in the study participants.

5. Conclusions

In conclusion, vitD deficiency is more common among Canadian immigrants than non-immigrants. Immigrants originating from African (Algeria and Morocco) and Asian (Lebanon) countries have a particularly low mean of S-25(OH)D. This study highlights ethnicity as a pivotal predictor of immigrants' lower S-25(OH)D levels; the Japanese, Arab, and Southeast Asian ethnic groups have a high prevalence of vitD deficiency. Short-term prevention strategies in community and clinical settings may be warranted, including vitD supplementation and awareness for people at higher risk. A long-term intervention plan may include developing/updating Canadian immigrant guidelines to incorporate evidence-based improvement strategies for vitD implementation.

Author Contributions: S.Y. and G.A.W. conceived the study. With close supervision from G.A.W., S.Y. managed the data, verified the analytical methods, and prepared the tables and figures. A.H. verified the underlying data at the Research Data Center. S.Y. and M.F. interpreted the results and prepared the final draft. All authors including D.M., I.C. and M.P. contributed to the design and analysis of the research, and the substantive review of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025). The CHMS was approved by the Health Canada Research Ethics Board.

Informed Consent Statement: Written consents were collected by Statistics Canada from all participants for a personal interview, physical measures, and biospecimens collection.

Data Availability Statement: Data described in the manuscript, codebook, and analytic code will not be made publicly available because the data are confidential national survey data hosted by Statistics Canada.

Acknowledgments: The authors acknowledge the team from the Carleton, Ottawa, Outaouais Local Research Data Centre for assistance with access to CHMS data. CHMS data were obtained and supported by funding to the Canadian Research Data Centre Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. Although the research and analysis were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Conflicts of Interest: The authors declare no personal or financial conflicts of interest.

Appendix A

Appendix A: Supporting information regarding the steps used to combine Cycles 3 and 4, and detailed information about the calculation of the variables of interest (Table A1).

Table A1. Variables of interest in Cycles 3 and 4 of the Canadian Health Measures Survey.

Variable	Description
Dependent variable	We used the contentious variable serum 25(OH)D (mmol/L). We categorized vitD status using the following cut-offs for S-25(OH)D: (<30 (nmol/L); (<50 (nmol/L); (<75 (nmol/L); and (≥75 (nmol/L). First, <30 nmol/L is used to identify deficient people. Second, (<50 nmol/L) is a cut-off for the insufficient 25(OH) D, which includes the deficient and insufficient people (it is an accumulating value and not range for the insufficient people). Third, (<75 nmol/L) is a cut-off and accumulating value for deficient, insufficient, and sufficient. Fourth (≥75 (nmol/L), it is the "no added value" or the "optimal" as defined by IOM or other experts [11–13]. Moreover, we used ranges of S-25(OH)D for the above mentioned cut-offs (<30 nmol/L; 30–49 nmol/L; 50–74 nmol/L and ≥75 nmol/L) for sub-groups of participants.

Table A1. *Cont.*

Variable	Description
Independent variables	
Immigration status	Landed immigrant (yes, no).
Age at time of immigration	Age at immigration was categorized as <18 years or ≥18 years.
Time since immigration	We used the continuous variable "length of time since first came to live in Canada" to categorize time since imigration at two cutoff points (≤5 years and >5 years; ≤10 years and >10 years). We used these points as indications of recent immigrants and long-term immigrants.
Sex	Male/female.
Age	Contentious and categorical variables.
Education	Education was classified as ≤secondary school or >secondary school.
Household income	Household income was derived and imputed by Statistics Canada. The contentious variable and categorical variables (<50,000, 50,000–100,000, and >100,000) were used as appropriate.
Body mass index	Calculated as weight divided by height squared (kg/m^2). We used body mass index norms for adults (≥18 years) based on national standards for weight classification [30]. For children (3–17 years), body mass index was classified according to World Health Organization percentiles [31].
Smoking	We categorized smoking status into two groups (former/non-smoker vs. current smoker).
Alcohol	We categorized alcohol consumption into two groups (former/non-drinker vs. current drinker).
Vitamin D-containing supplements/medications	All prescription medications, over-the-counter, and herbal remedies taken in the past month (including vitD supplements and medications) were recorded in the CHMS data. The Anatomical Therapeutic Chemicals (ATCs) is a system that classifies products according to the organ and their chemical, pharmacological, and therapeutic properties. The vitD -related ATC codes were selected (A11CC01–05). These ATC codes represent ergocalciferol (vitD 2), dihydrotachysterol (synthetic vitD analog), alfacalcidol (analog of vitD), calcitriol, and cholecalciferol (vitD 3). Users of any of these were recorded as "yes," non-users as "no," and not respondents as "missing."
Dietary intake	The CHMS collected dietary intake of different types of each item (red meat, liver, fish, egg, milk, cheese, yogurt, margarine) based on the previous month's consumption. Statistics Canada prepared derived variables for each item to describe the number of times that item had been consumed/year. These derived variables were used to calculate consumption per week or day as needed. Different types of each item were merged into a single category. For example, all kinds of milk (plain, flavored, omega-3) were merged as "all milk." The same procedure was used for "all meats" (e.g., red meat, liver, sausage, hotdog), as well as "all cheese," "all yogurt," "all eggs," and "all margarine." Another category was used for all dairy products, called "all diary." We also used fish consumption in the past two months as (yes vs. no). Values of ≤1 time/week vs. >1 time/week were used for all categories, except all milk and all dairy, which used ≤7 times/week vs. >7 times/week.
Calcium and phosphorus	Contentious variables (mmol/L).
Pregnancy	Pregnancy was classified as Yes or No.
Ethnicity	Broadly, ethnicity was classified into two main groupings as white or non-white. Statistics Canada categorized non-white into the 12 largest ethnic groups (Aboriginal, South Asian, Chinese, Black, Filipino, Latin American, Arab, South East Asian, West Asian, Korean, Japanese, Multiple ethnicities), and another category for all other ethnicities.
Season of blood sampling	The season variable was created based on the derived variable of "month of blood sampling." We categorized the season as winter (December–February), spring (March–May), summer (June–August), and fall (September–November).
Regions of birth	We used five regions: Canada and North America; South and Central America and the Caribbean; Europe; Africa; and Asia.

Table A1. *Cont.*

Variable	Description
Countries of birth	We used the geographic classifications of Statistics Canada to identify the country of birth for all CHMS participants (153 countries) [58]. We ranked and selected the top 20 countries based on the number of participants (≥30 participants from each). These countries were Canada, China, the US, France, Jamaica, the UK, Algeria, Mexico, Pakistan, the Netherlands, India, the Philippines, Romania, Hong Kong, Germany, Colombia, Morocco, Italy, Iran, and Lebanon. We combined all other countries in one category, "Other," and combined the 153 countries (excluding Canada) in another class to represent all foreign-born immigrants.
Sun exposure (10 am to 4 pm)	Sun exposure was classified as <30 min\day or ≥30 min\day.
Sunscreen application	Sunscreen application was classified as yes or no.
Clothing type	The clothing type was based on coverage and classified as yes or no. Yes indicated typically covered (face, ears, neck or arms and legs).
Physical activity	Physical activity for adults (≥18 years) was calculated based on the Canadian Physical Activity Guidelines (CPAG). The CPAG recommendation for adults is to accumulate at least 150 min of moderate-to-vigorous intensity aerobic physical activity per week, in bouts of ≥10 min. The CPAG recommendation for children (5–17 years) is to accumulate at least 60 min of moderate-to-vigorous intensity physical activity daily for at least three days per week [32].
Traveled to a sunny/warmer place (in the past two months)	Travelling to a sunny/warmer place in the past two months was classified as yes or no.
Skin pigmentation (melanin levels)	Melanin is the component that gives skin its natural color. Melanin levels were measured from the back of the hand three times; a fourth measurement was required if the difference between the first three melanin values deviated by more than 10 units. The final average calculated by Statistics Canada indicates the absolute index values of melanin, where the higher the value, the more melanin present in the epidermal. The device used for measurement was the DSM II ColorMeter (Cortex Technology, Hadsund, Denmark).

Appendix A.1. Combining Cycles 3 and 4

The CHMS is the first national population-based survey on vitamin D (vitD) conducted in Canada. Data were collected in six cycles biannually between 2007–2019. Compared with other cycles, Cycle 3 (2012–2013) and Cycle 4 (2014–2015) are considered the most thematically consistent in terms of vitD-related sociodemographic characteristics, lifestyle factors, vitD-rich foods consumption, and behavioral, environmental, and biological determinants. Immigrant status was defined as being born outside Canada [27]. In this study, we combined data from Cycles 3 and 4 to increase the sample size and provide a more stable and precise estimate of sampling variability at the national level than was possible using a single data cycle estimate. The combination of the two cycles followed Statistics Canada's guideline for combining CHMS cycles. As recommended, we used Bootstrap 1–Bootstrap 500, full-weight or applicable weight, and the required degrees of freedom to correct variance estimations. Therefore, the pre-specified combined full-sample weights and degrees of freedom for the two cycles were used in our analyses. The single-cycle weight was dropped from the dataset as it was a cycle-specific weight. The combined response rate (response rate for all study components, such as household visit, blood samples, and activity monitor) at the Canadian level for Cycle 3 was 51.7%, and that for Cycle 4 was 53.7% [33,34].

Appendix A.2. Population, Comparators, Measures, and Outcome

The population of interest in this study was first-generation Canadian immigrants (foreign-born) from different origins and ethnicities. The comparators were non-immigrants (native-born population) and the white ethnic grouping. The S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, Minnesota, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. The inter-assay coefficients of variation for the S-25(OH)D was 13.0% and the precision for <20 nmol/L, 20–100 nmol/L and >100 nmol/L levels were 15.0%, 10.0% and 12.0%, respectively [45].

The results are presented as weighted means or proportions only. The weighted results and proportions were based on the total number of 11,579 participants. The number of participants for each group cannot be published because of Statistics Canada's restrictions policy relates to publishing weighted results. The weighting technique for complex survey results refers to statistical adjustments that have been used to correct and improve the accuracy of the survey estimates. The survey weights adjust for unequal probabilities of selection that often have occurred during sampling design and to help compensate for survey non-response weights. Thus, by using the survey weights to create estimates should yield approximately unbiased national prevalence estimates and reduce non-response bias that can be introduced due to random missing values. The study outcomes were the serum 25(OH)D levels and vitD status.

Appendix A.3. Variables of Interest

The data manipulation and all derived variables were consistent with Statistics Canada's instructions based on the specific cycle user guide, data codebook, instructions for combining more than one cycle, and the derived variable specifications [33]. The CHMS microdata are hosted in secure centers overall in Canada. These data were accessed and analyzed at the Carleton, Ottawa, Outaouais Local Research Data Centre (COOLRDC), located in the Morisset Library at the University of Ottawa.

Appendix B

Appendix B: supporting information including (Tables A2–A6).

This Appendix sets out the steps followed in combining Cycles 3 and 4 of the Canadian Health Measures Survey (CHMS), variables of interest, critical data manipulation stages, and other methodological aspects.

This Appendix contains supplementary material for the manuscript entitled "*Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study using the Canadian Health Measures Survey.*"

Table A2. Weighted prevalence and mean S-25(OH)D (nmol/L) levels and basic study characteristics using Cycles 3 and 4 of Canadian Health Measures Survey data.

		Cycle 3 (49.52%) %	**Cycle 4 (50.48%)** %	**Total (100%)** %
Immigration status	Immigrant	24.5	19.38	21.90
Ethnic group	White	75.10	78.87	76.98
Sex	Female	50.00	50.10	50.08
Age (years)	<5	2.47	2.14	2.30
	5–11	7.92	8.17	8.04
	12–17	7.58	7.21	7.39
	18–64	70.70	70.29	70.54
	>64	11.20	12.20	11.72
Household income (CAD)	<50,000	38.10	32.91	35.45
	50,000–100,000	36.00	37.26	36.61
	>100,000	26.00	29.84	27.93
S-25(OH)D status (nmol/l)	<50	65.04	62.27	63.64
Weighted Mean		Mean (SE)	Mean (SE)	Mean (SE)
	Age (years)	39.08 (0.15)	39.35 (0.09)	39.23 (0.085)
	S-25(OH)D (nmol/L)	61.29 (2.78)	59.16 (1.99)	60.28 (1.69)

SE, standard error.

Table A3. Weighted prevalence of vitamin D-rich food/fish consumption for immigrants and non-immigrants using Cycles 3 and 4 of Canadian Health Measures Survey data.

		Non-Immigrants (78.9%), %	Immigrants (21.9%), %	All Participants (100%), %	*p*-Value
All meats (red meat, liver, hotdog, and sausage)	>1 time/week	90.47	78.72	87.89	<0.001
All eggs (yolk/omega-3)	>1 time/week	59.68	66.95	61.26	0.067
All milk (plain, flavored, and omega-3)	>7 times/week	54.63	48.38	53.27	0.027
All cheese (cottage and other)	>1 time/week	86.70	63.26	81.57	<0.001
All yogurt	>1 time/week	72.19	70.15	71.75	0.577
All dairy products (milk, yogurt, and cheese)	>7 times/week	83.38	75.38	81.64	<0.001
All margarine (plain and omega-3)	>1 time/week	84.11	70.95	81.90	0.007
Fortified juice with calcium/vitamin D	>1 time/week	7.01	6.12	6.81	0.452
Fish consumption/past 2 months	Yes (No [†])	25.18	17.09	23.43	0.046

Reference values: $\leq$1 time/week; $\leq$7 times/week. [†] Reference value; *p*-values $\leq$ 0.05.

Table A4. Weighted means for S-25(OH)D (nmol/L) and vitamin D status by sociodemographic and lifestyle factors using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)			S-25(OH)D Status			
		Mean (SE)	**(95% CI)**	***p*-Value**	**<30 (nmol/L (10.3%),%**	**<50 (nmol/L (63.64%),%**	**<75 (nmol/L (76.1%),%**	**≥75 (nmol/L (23.9%),%**
Household income (CAD)	<50,000 †	56.18 (1.90)	-		13.95	45.10	79.43	20.57
	50,000–100,000	61.44 (1.81)	(−7.73, −2.79)	<0.001	9.67	33.14	76.02	23.98
	>100,000	63.66 (1.79)	(−9.97, −4.98)	<0.001	6.53 ***	29.64 ***	72.09	27.91 **
Education	≤Secondary school †	59.41 (1.64)			9.57	36.81	77.58	22.42
	>Secondary school	61.00 (1.86)	(−3.59, 0.41)	0.113	10.87	35.83	74.97	25.03
Pregnancy	No†	60.35 (2.15)	-		11.72	36.88	75.29	24.71
	Yes	51.22 (7.40)	(−6.69, 24.94)	0.244	2.11	45.70	93.21	6.79 *
Smoking habits	Former/non-smoker †	61.59 (1.66)	-		9.98	34.12	73.82	26.18
	Current smoker	53.09 (2.12)	(5.74, 11.24)	<0.001	14.88 *	50.71 ***	85.02	14.98 ***
Alcoholic beverages	Former/non-drinker †	54.25 (2.17)	-		15.72	38.15	81.44	18.56
	Current drinker	61.33 (1.67)	(−10.49, 3.66)	<0.001	9.73 **	34.70 ***	74.70	25.30 **
Meet the physical activity recommendations	No †	58.79 (1.54)	-		11.32	39.34	77.91	22.09
	Yes	63.80 (2.34)	(−8.26, 1.76)	0.004	8.01	29.54 ***	72.86	27.14 *
Clothing	Uncovered †	62.07 (1.69)	-		8.23	31.13	74.85	25.15
	Typically covered	57.91 (2.00)	(1.46, 6.85)	0.004	12.86 **	42.58 ***	77.86	22.14

† Reference value; SE, standard error; CI, confidence interval; BMI, body mass index. *p*-values: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Table A5. Weighted means for S-25(OH)D (nmol/L) by season and month of blood test using Cycles 3 and 4 of Canadian Health Measures Survey data.

		S-25(OH)D (nmol/L)		*p*-Value
		Mean (SE)	(95% CI)	
Season	Winter †	53.80 (2.47)	-	
	Spring	54.63 (1.41)	(−7.16, 5.49)	0.786
	Summer	66.13 (2.38)	(−18.50, −6.16)	<0.001
	Fall	66.00 (3.63)	(−20.59, −3.83)	0.006
Month	January †	57.67 (9.25)	-	
	February	47.13 (6.17)	(−25.73, 4.65)	0.164
	March	52.02 (9.57)	(−28.63, 18.86)	0.674
	April	57.31 (1.64)	(−23.46, 3.10)	0.126
	May	55.00 (2.17)	(−21.38, 5.63)	0.240
	June	63.34 (8.61)	(−38.14, 5.73)	0.140
	July	68.02 (5.41)	(−37.88, −3.89)	0.018
	August	67.78 (7.31)	(−40.77, −0.53)	0.045
	September	72.08 (10.24)	(−49.86, −0.04)	0.050
	October	67.34 (5.39)	(−37.99, −2.42)	0.028
	November	57.52 (2.80)	(−24.80, −4.02)	0.149
	December	59.20 (13.18)	(−42.89, 18.75)	0.425

† Reference value; SE, standard error; CI, confidence interval; *p*-values ≤ 0.05.

Table A6. Weighted mean S-25(OH)D concentrations (nmol/L) by immigration status and season using Cycles 3 and 4 of Canadian Health Measures Survey data.

		Non-Immigrant †	Immigrant		
		Mean (SE)	Mean (SE)	(95% CI)	*p*-Value
Season	Winter	55.36 (2.33)	47.79 (4.55)	(−0.67, 15.82)	0.070
	Spring	56.94 (1.62)	47.71 (3.07)	(2.27, 16.19)	0.012
	Summer	70.03 (2.23)	55.21 (1.76)	(9.28, 20.36)	<0.001
	Fall	68.11 (3.55)	54.87 (3.95)	(8.00, 18.47)	<0.001

† Reference value; SE, standard error; CI, confidence interval; *p*-values ≤ 0.05.

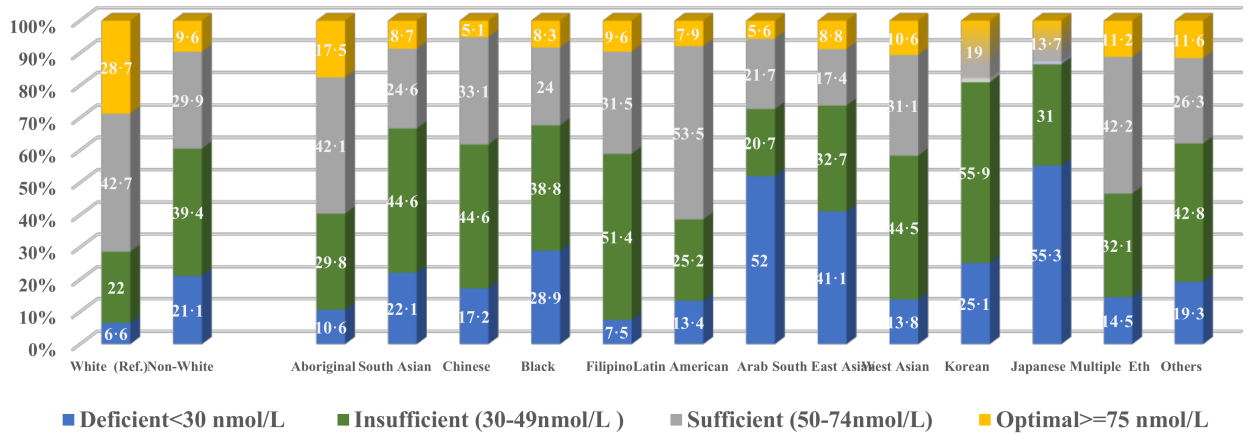


Figure A1. Weighted prevalence of S-25(OH)D status for immigrants from different ethnic groups using Cycles 3 and 4 of Canadian Health Measures Survey data.

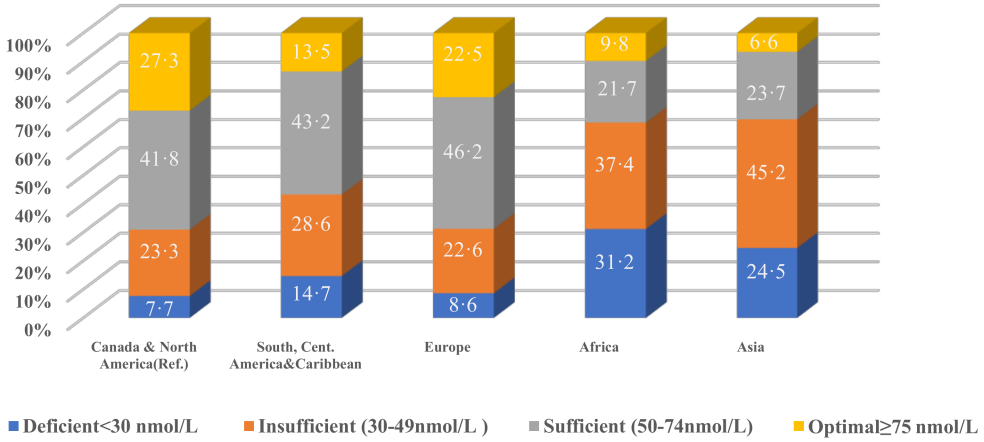


Figure A2. Weighted prevalence of S-25(OH)D status for immigrants by region of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

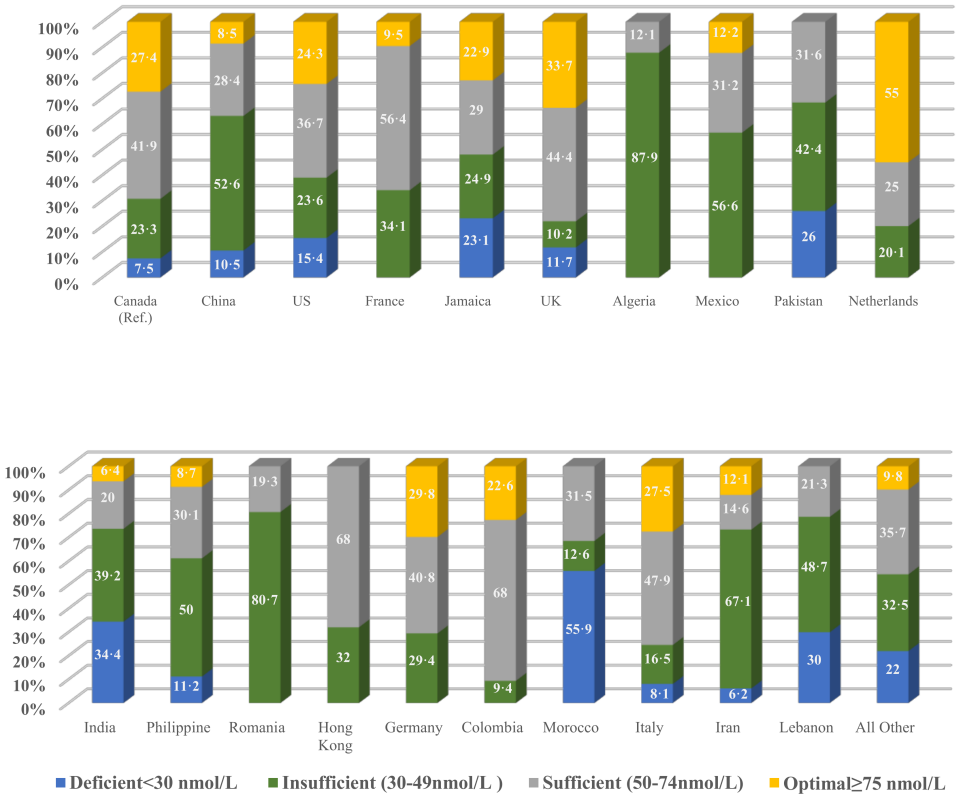


Figure A3. Weighted prevalence of S-25(OH)D status by country of birth using Cycles 3 and 4 of Canadian Health Measures Survey data.

References

1. Charoenngam, N.; Shirvani, A.; Holick, M.F. Vitamin D for skeletal and non-skeletal health: What we should know. *J. Clin. Orthop. Trauma* **2019**, *10*, 1082–1093. [CrossRef]
2. Shin, S.Y.; Kwon, M.J.; Song, J.; Park, H.; Woo, H.Y. Measurement of Serum Total Vitamin D (25-OH) Using Automated Immunoassay in Comparision With Liquid Chromatography Tandem-Mass Spectrometry. *J. Clin. Lab. Anal.* **2013**, *27*, 284–289. [CrossRef]
3. Atef, S.H. Vitamin D assays in clinical laboratory: Past, present and future challenges. *J. Steroid Biochem. Mol. Biol.* **2018**, *175*, 136–137. [CrossRef] [PubMed]
4. Martens Immunoassay for Free Vitamin D. 2018. Available online: https://patentimages.storage.googleapis.com/57/7e/64/9c4548d4ed8ce1/US9897615.pdf (accessed on 24 February 2021).

5. Nowson, C.A.; McGrath, J.J.; Ebeling, P.R.; Haikerwal, A.; Daly, R.M.; Sanders, K.M.; Seibel, M.J.; Mason, R.S. Vitamin D and health in adults in Australia and New Zealand: A position statement. *Med. J. Aust.* **2012**, *196*, 686–687. [CrossRef]
6. Heaney, R.P.; Recker, R.R.; Grote, J.; Horst, R.L.; Armas, L.A. Vitamin D3 is more potent than vitamin D2 in humans. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E447–E452. [CrossRef] [PubMed]
7. De Boer, I.H.; Kestenbaum, B.; Shoben, A.B.; Michos, E.D.; Sarnak, M.J.; Siscovick, D.S. 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. *J. Am. Soc. Nephrol.* **2009**, *20*, 1805–1812. [CrossRef]
8. Spiro, A.; Buttriss, J. Vitamin D: An overview of vitamin D status and intake in E urope. *Nutr. Bull.* **2014**, *39*, 322–350. [CrossRef]
9. Zmijewski, M.A. Vitamin D and Human Health. *Int. J. Mol. Sci.* **2019**, *20*, 145. [CrossRef] [PubMed]
10. Mithal, A.; Wahl, D.A.; Bonjour, J.-P.; Burckhardt, P.; Dawson-Hughes, B.; Eisman, J.A.; Fuleihan, G.E.-H.; Josse, R.G.; Lips, P.; Morales-Torres, J. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos. Int.* **2009**, *20*, 1807–1820. [CrossRef]
11. Ross, A.; Taylor, C.; Yaktine, A.; Del Valle, H. *Dietary Reference Intakes: Calcium and Vitamin D. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board*; National Academy of Sciences: Washington, DC, USA, 2011.
12. Vieth, R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/mL). *Best Pract. Res. Clin. Endocrinol. Metab.* **2011**, *25*, 681–691. [CrossRef]
13. Dawson-Hughes, B. *Vitamin D Deficiency in Adults: Definition, Clinical Manifestations, and Treatment*; UpToDate: Waltham, MA, USA, 2014.
14. Pham, T. Vitamin D Status of Immigrant and Ethnic Minority Children Ages 2 to 5 y in Montréal. Master's Thesis, McGill University, Montreal, QC, Canada, 2012.
15. Janz, T.; Pearson, C. *Vitamin D Blood Levels of Canadians*; Statistics Canada Ottawa (Canada): Ottawa, ON, Canada, 2013.
16. Yousef, S.; Elliott, J.; Manuel, D.; Colman, I.; Papadimitropoulos, M.; Hossain, A.; Leclair, N.; Wells, G.A. Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations—A systematic review and meta-analysis. *Syst. Rev.* **2019**, *8*, 211. [CrossRef]
17. Cashman, K.D.; Dowling, K.G.; Škrabáková, Z.; Gonzalez-Gross, M.; Valtueña, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Mølgaard, C. Vitamin D deficiency in Europe: Pandemic? *Am. J. Clin. Nutr.* **2016**, *103*, 1033–1044. [CrossRef]
18. Martin, C.A.; Gowda, U.; Renzaho, A.M. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. *Nutrition* **2016**, *32*, 21–32. [CrossRef]
19. Eggemoen, Å.R.; Knutsen, K.V.; Dalen, I.; Jenum, A.K. Vitamin D status in recently arrived immigrants from Africa and Asia: A cross-sectional study from Norway of children, adolescents and adults. *BMJ Open* **2013**, *3*, e003293. [CrossRef] [PubMed]
20. Chui, T.; Statistics Canada. *Immigration and Ethnocultural Diversity in Canada: National Household Survey*; Statistics Canada: Ottawa, ON, Canada, 2011.
21. Salant, T.; Lauderdale, D.S. Measuring culture: A critical review of acculturation and health in Asian immigrant populations. *Soc. Sci. Med.* **2003**, *57*, 71–90. [CrossRef]
22. Zhu, L. Depression risks and correlates among different generations of Chinese Americans: The effects of relationships with friends and relatives. *Soc. Sci.* **2017**, *6*, 56. [CrossRef]
23. Stephens, W.; Klimiuk, P.; Warrington, S.; Taylor, J.; Berry, J.; Mawer, E. Observations on the natural history of vitamin D deficiency amongst Asian immigrants. *QJM Int. J. Med.* **1982**, *51*, 171–188.
24. Stern, P.J. Generational differences. *J. Hand Surg.* **2002**, *27*, 187–194. [CrossRef]
25. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Bull. World Health Organ.* **2007**, *85*, 867–872. [CrossRef] [PubMed]
26. Day, B.; Langlois, R.; Tremblay, M.; Knoppers, B.-M. Canadian Health Measures Survey: Ethical, legal and social issues. *Health Rep.* **2007**, *18*, 37–51. [PubMed]
27. Ng, E. Canadian Health Measures Survey: A tool for immigrant health research? *Health Rep.* **2015**, *26*, 3. [PubMed]
28. Statistics Canada. Canadian Health Measures Survey, Cycle 4, 2014–2015—Privacy Impact Assessment Summary. Available online: https://www.statcan.gc.ca/eng/about/pia/chmsc4 (accessed on 14 February 2021).
29. Statistics Canada. 2012–2013 Canadian Health Measures Survey, Cycle 3—Privacy Impact Assessment. Available online: https://www.statcan.gc.ca/eng/about/pia/chmsc3 (accessed on 14 February 2021).
30. Health Canada. *Canadian Guidelines for Body Weight Classification in Adults—Quick Reference Tool for Professionals*; Health Canada: Ottawa, ON, Canada, 2003.
31. Onis, M.d.; Onyango, A.W.; Borghi, E.; Siyam, A.; Nishida, C.; Siekmann, J. Development of a WHO growth reference for school-aged children and adolescents. *Bull. World Health Organ.* **2007**, *85*, 660–667. [CrossRef] [PubMed]
32. Canadian Physical Activity. *Sedentary Behaviour Guidelines*; Canadian Society for Exercise Physiology: Ottawa, ON, Canada, 2012.
33. Statistics Canada. Canadian Health Measures Survey (CHMS)Data User Guide: Cycle 3. 2015. Available online: https://usermanual.wiki/Pdf/CHMSUserGuideCycle3E.484319040/help (accessed on 24 February 2021).
34. Statistics Canada. Canadian Health Measures Survey (CHMS)—Cycle 4. Available online: https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&Id=148760 (accessed on 25 January 2021).
35. Hilger, J.; Friedel, A.; Herr, R.; Rausch, T.; Roos, F.; Wahl, D.A.; Pierroz, D.D.; Weber, P.; Hoffmann, K. A systematic review of vitamin D status in populations worldwide. *Br. J. Nutr.* **2014**, *111*, 23–45. [CrossRef]

36. Pludowski, P.; Grant, W.B.; Bhattoa, H.P.; Bayer, M.; Povoroznyuk, V.; Rudenka, E.; Ramanau, H.; Varbiro, S.; Rudenka, A.; Karczmarewicz, E. Vitamin D status in central Europe. *Int. J. Endocrinol.* **2014**, *2014*. [CrossRef] [PubMed]
37. Lips, P. Vitamin D status and nutrition in Europe and Asia. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 620–625. [CrossRef]
38. Alshahrani, A.A. Vitamin D Deficiency and Possible Risk Factors among Middle Eastern University Students in London, Ontario, Canada. Master's Thesis, The University of Western Ontario, London, ON, Canada, 2014.
39. McCormack, D.; Mai, X.; Chen, Y. Determinants of vitamin D supplement use in Canadians. *Public Health Nutr.* **2017**, *20*, 1768–1774. [CrossRef]
40. Knoss, R.; Halsey, L.G.; Reeves, S. Ethnic dress, vitamin D intake, and calcaneal bone health in young women in the United Kingdom. *J. Clin. Densitom.* **2012**, *15*, 250–254. [CrossRef]
41. Ojah, R.C.; Welch, J.M. Vitamin D and musculoskeletal status in Nova Scotian women who wear concealing clothing. *Nutrients* **2012**, *4*, 399–412. [CrossRef] [PubMed]
42. Mark, S. Vitamin D Status and Recommendations to Improve Vitamin D Status in Canadian Youth. Master's Thesis, McGill University, Montreal, QC, Canada, 2010.
43. Naugler, C.; Zhang, J.; Henne, D.; Woods, P.; Hemmelgarn, B.R. Association of vitamin D status with socio-demographic factors in Calgary, Alberta: An ecological study using Census Canada data. *BMC Public Health* **2013**, *13*, 316. [CrossRef]
44. Ghasemian, R.; Shamshirian, A.; Heydari, K.; Malekan, M.; Alizadeh-Navaei, R.; Ebrahimzadeh, M.A.; Jafarpour, H.; Shahmirzadi, A.R.; Khodabandeh, M.; Seyfari, B. The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis. *MedRxiv* **2020**. [CrossRef]
45. Munasinghe, L.L.; Yuan, Y.; Willows, N.D.; Faught, E.L.; Ekwaru, J.P.; Veugelers, P.J. Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010. *Br. J. Nutr.* **2017**, *117*, 457–465. [CrossRef]
46. Wang, L.; Manson, J.E.; Buring, J.E.; Lee, I.-M.; Sesso, H.D. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension* **2008**, *51*, 1073–1079. [CrossRef]
47. Thuesen, B.; Husemoen, L.; Fenger, M.; Jakobsen, J.; Schwarz, P.; Toft, U.; Ovesen, L.; Jørgensen, T.; Linneberg, A. Determinants of vitamin D status in a general population of Danish adults. *Bone* **2012**, *50*, 605–610. [CrossRef]
48. Renzaho, A.M.; Halliday, J.A.; Nowson, C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review. *Nutrition* **2011**, *27*, 868–879. [CrossRef] [PubMed]
49. Neale, R.; Khan, S.; Lucas, R.; Waterhouse, M.; Whiteman, D.; Olsen, C. The effect of sunscreen on vitamin D: A review. *Br. J. Dermatol.* **2019**, *181*, 907–915. [CrossRef] [PubMed]
50. Young, A.; Narbutt, J.; Harrison, G.; Lawrence, K.; Bell, M.; O'Connor, C.; Olsen, P.; Grys, K.; Baczynska, K.; Rogowski-Tylman, M. Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. *Br. J. Dermatol.* **2019**, *181*, 1052–1062. [CrossRef]
51. Brooks, S.P.; Greene-Finestone, L.; Whiting, S.; Fioletov, V.E.; Laffey, P.; Petronella, N. An analysis of factors associated with 25-hydroxyvitamin D levels in white and non-white Canadians. *J. AOAC Int.* **2017**, *100*, 1345–1354. [CrossRef] [PubMed]
52. Nimitphong, H.; Holick, M.F. Vitamin D status and sun exposure in Southeast Asia. *Derm. Endocrinol.* **2013**, *5*, 34–37. [CrossRef]
53. Sanou, D.; O'Reilly, E.; Ngnie-Teta, I.; Batal, M.; Mondain, N.; Andrew, C.; Newbold, B.K.; Bourgeault, I.L. Acculturation and nutritional health of immigrants in Canada: A scoping review. *J. Immigr. Minority Health* **2014**, *16*, 24–34. [CrossRef]
54. Carlberg, C. Nutrigenomics of vitamin D. *Nutrients* **2019**, *11*, 676. [CrossRef]
55. Leandro, A.; Rocha, M.; Cardoso, C.; Bonecini-Almeida, M. Genetic polymorphisms in vitamin D receptor, vitamin D-binding protein, Toll-like receptor 2, nitric oxide synthase 2, and interferon-γ genes and its association with susceptibility to tuberculosis. *Braz. J. Med Biol. Res.* **2009**, *42*, 312–322. [CrossRef] [PubMed]
56. Aucoin, M.; Weaver, R.; Thomas, R.; Jones, L. Vitamin D status of refugees arriving in Canada: Findings from the Calgary Refugee Health Program. *Can. Fam. Physician* **2013**, *59*, e188–e194. [PubMed]
57. Baauw, A.; Kist-van Holthe, J.; Slattery, B.; Heymans, M.; Chinapaw, M.; van Goudoever, H. Health needs of refugee children identified on arrival in reception countries: A systematic review and meta-analysis. *BMJ Paediatr. Open* **2019**, *3*, e000516. [CrossRef] [PubMed]
58. Statistics, C. Standard Classification of Countries and Areas of Interest (SCCAI). Available online: https://publications.gc.ca/site/eng/9.856211/publication.html (accessed on 24 February 2020).

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 January 2023
DOI 10.3389/fmed.2022.992554

OPEN ACCESS

EDITED BY
Devinder Mohan Thappa,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

REVIEWED BY
Malathi Munisamy,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India
Manuel Valdebran Canales,
Medical University of South Carolina, United States

*CORRESPONDENCE
Said Yousef

SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 26 July 2022
ACCEPTED 16 December 2022
PUBLISHED 09 January 2023

CITATION
Yousef S, Papadimitropoulos M, Faris M, Hasan H, Hossain A, Colman I, Manuel D and Wells GA (2023) Melanin levels in relation to vitamin D among first-generation immigrants from different ethnic groups and origins: A comparative national Canadian cross-sectional study. *Front. Med.* 9:992554. doi: 10.3389/fmed.2022.992554

Melanin levels in relation to vitamin D among first-generation immigrants from different ethnic groups and origins: A comparative national Canadian cross-sectional study

Said Yousef[1,2]*, Manny Papadimitropoulos[3,4], MoezAlIslam Faris[5], Hayder Hasan[5], Alomgir Hossain[1,6], Ian Colman[1], Douglas Manuel[6,7,8] and George A. Wells[1,2]

[1]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada, [2]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada, [3]Eli Lilly Canada Inc., Toronto, ON, Canada, [4]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [5]Department of Clinical Nutrition and Dietetics, College of Health Sciences, Research Institute of Medical and Health Sciences, University of Sharjah, Sharjah, United Arab Emirates, [6]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [7]Ottawa Hospital Research Institute, Ottawa, ON, Canada, [8]Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada

Introduction: Immigrants to Western countries tend to have darker skin than native-born populations. We examined the relationship between skin melanin and serum vitamin D (vitD) [S-25(OH)D] levels and explored whether melanin levels explained S-25(OH)D variations between immigrants and native-born Canadians. This study offers novel findings as no such study has been conducted.

Methods: We used a national cross-sectional population-based design with data from the Canadian Health Measures Survey (CHMS). Skin melanin levels among first-generation immigrants based on their ethnicity and origin/country of birth were compared with white and native-born populations. We assessed the association between S-25(OH)D and melanin after adjusting for independent variables related to S-25(OH)D, melanin level, and immigration status.

Results: Of 11,579 participants, 21.9% were immigrants aged 3–79 years (mean age 39.23 years). Compared with non-immigrants, immigrants had lower S-25(OH)D levels (mean: 51.23 vs. 62.72; 95% CI: 8.37, 14.62; $P < 0.001$) but higher melanin levels (mean [*SE*]: 17.08 [0.25] vs. 16.29 [0.29]; 95% CI: −1.29, −0.281; $P = 0.004$). Melanin did not differ by length of stay in Canada but was weakly positively correlated ($r = 0.088$, $P < 0.001$) with S-25(OH)D. Sex (male), age (≥18 years), summer/fall seasons, sunlight exposure, sunscreen non-use, smoking, and alcohol consumption were associated with higher melanin levels, whereas indoor tanning use was not.

Conclusion: Skin melanin levels were associated with sociodemographic and behavioral characteristics. Immigrants had higher melanin levels, but melanin did not differ by length of stay in Canada. The weak positive correlation between melanin and S-25(OH)D suggested confounding factors may impact the relationship between melanin levels, S-25(OH)D, and immigration status.

KEYWORDS

melanin, serum vitamin D, 25(OH)D, immigrants, indoor tanning

Highlights

- Immigrants to Western countries have higher melanin (darker skin) and lower S-25(OH)D levels than native-born populations, but it remains unclear if melanin levels explain variations in S-25(OH)D between first-generation immigrants (based on ethnicity/country of birth) and native-born populations.
- We used national Canadian data that captured the ethnocultural diversity of immigrants from more than 150 countries and over 13 major ethnic groups to investigate whether melanin levels explained variations in S-25(OH)D between immigrants and native-born populations.
- Immigrants had higher melanin levels than non-immigrants, but there was no difference in melanin by immigrants' length of stay in Canada.
- Melanin was weakly positively correlated with S-25(OH)D, with higher melanin levels associated with sociodemographic and environmental factors but not with indoor tanning use.
- The robust associations between these factors and both skin melanin and S-25(OH)D levels highlight the potential of exploring the role of ethnicity and sociodemographic factors in designing national intervention programs to improve vitD status.

Introduction

Melanin is a natural pigment present in the skin that formulates skin color and that of other body parts such as hair and eyes (1, 2). It is naturally produced in the human body and hair follicles, mainly by melanocytes. The degree of skin pigmentation depends on the degree of gene expression that controls the quality and quantity of melanin (1–4). Melanin has many physiological benefits in maintaining health, with the most documented being that it acts as a sunscreen and protects the body from harmful ultraviolet (UV) radiation (3, 4). Previous studies suggested that melanin may reduce body inflammation, prevent liver injuries and play a role in the immune system (5–7).

Vitamin D (vitD) is an essential fat-soluble nutrient with diverse biological functions that extend beyond the classical function of bone mineralization and skeletal maintenance. These extra functions include combating several chronic diseases, such as cardiovascular disease, hypertension, diabetes, cancer, and dermatological and autoimmune diseases (8–13). Other non-classical functions of vitD include regulation of cellular differentiation, proliferation, apoptosis, and adaptive and innate immunity (14). Following the discovery of the vitD receptor and several genetic polymorphisms that modulate the levels of vitD in the human body, increased attention has been directed toward genetic variations in different ethnic groups and how they variably interact in determining vitD levels (15).

Skin exposure to sunlight is the primary source of vitD3 synthesis (cutaneous synthesis) (16, 17), which primarily occurs in the upper skin layers. Because of its function as a biological shield against UV radiation, melanin inhibits cutaneous vitD3 synthesis. This is because dark skin pigmentation is mainly based on the eumelanin type (a dark brown/black bio-aggregate of melanin pigments derived from 5,6-dihydroxyindole-2-carboxylic acid and 5,6-dihydroxyindole) located in the basal layer of the epidermis (17, 18). Therefore, the higher melanin levels associated with dark skin require more sunlight exposure to produce sufficient vitD (19–21).

One in five Canadians is a first-generation immigrant and identified as foreign-born (22). Canada's population is expected to increase by approximately 1 million foreign-born residents every 3 years by 2035/2036 (23). Globally, immigrants to Western countries tend to have darker skin pigmentation than the native-born population of the host country. Moreover, darker-skinned immigrants in Canada and other Western countries have a high prevalence of vitD deficiency and insufficiency compared with Western people, with a deficiency prevalence of 19.3–80% among different ethnic minorities (9, 19, 22, 24).

In our previous analysis of Canadian Health Measures Survey (CHMS) data, melanin levels were identified and used by Statistics Canada as an indicator of skin pigmentation (i.e., higher ranks indicated darker skin). That study concluded that immigrants' ethnic variation was the main predictor of/explanatory factor for lower S-25(OH)D among immigrants

than among native-born Canadians. Other factors, including skin pigmentation (melanin level), were also associated with differences in S-25(OH)D levels (22). However, no previous study has examined the relationship between melanin levels and S-25(OH)D among immigrants based on their ethnicity and region/country of birth compared with non-immigrants. Although the relationship between the two outcomes (vitD and melanin) is well-established in the literature, this relationship has not been fully elucidated in the context of first-generation immigrants and inherent factors related to these immigrants. Therefore, the present study was designed to fill this knowledge gap and examine the relationship between melanin and vitD levels among first-generation immigrants from different ethnicities (more than 13 ethnicities) and origins or countries of birth (more than 153 countries) compared with native-born Canadians. Moreover, we evaluated whether melanin levels could explain the variations in S-25(OH)D between immigrants and native-born Canadians. We hypothesized that melanin levels varied among CHMS participants based on their ethnicity and country of origin, which may explain the variations in S-25(OH)D.

Materials and methods

Study design and participants

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) planning, implementation, and reporting guidelines (25). The study was part of a larger study investigating the association between vitD and health deterioration among first-generation immigrants in Canada (12, 22). We used Cycle 3 (2012–2013) and Cycle 4 (2014–2015) of the CHMS data. The CHMS is a national cross-sectional population-based survey conducted by Statistics Canada in collaboration with Health Canada and the Public Health Agency of Canada (26). The sample population weight was adjusted for age group and sex across Canada's five standard geographic regions: British Columbia, the Prairies, Ontario, Quebec, and the Atlantic Provinces (26, 27). All participants provided written informed consent, and the CHMS survey was approved by the Health Canada Research Ethics Board (26).

Measures

Melanin level (index value) was measured in CHMS data as an indicator of the level of skin pigmentation. In this study, we used the data for melanin as the outcome-dependent factor. Melanin levels were measured from the back of the hand three times; a fourth measurement was required if the difference between the first three melanin values deviated by more than 10 units. Melanin measurements were collected from each participant in the same visit. The final average calculated by Statistics Canada indicated the absolute index values of melanin. The higher the value, the more melanin is present in the epidermal and the darker the person's skin. The device used for measurement was the DSM II ColorMeter (Cortex Technology, Hadsund, Denmark) (28, 29). Most previous immigration studies did not report the degree of skin pigmentation, and many studies used ethnicity or immigrants' country of origin as a proxy indicator for skin color (19). However, we believe the measurement of skin melanin is a reliable indicator for skin pigmentation that enables investigation of correlations with S-25(OH)D among immigrants from different ethnicities and origins.

The S-25(OH)D level reflects total vitD intake from foods, supplements, and synthesis in the skin. We used mean S-25(OH)D as well as S-25(OH)D cut-off values to identify sufficient ($\geq$50 nmol/L) or insufficient ($<$50 nmol/L) vitD status as defined by the Institute of Medicine and other expert reports (20, 30–32). S-25(OH)D was measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, MN, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L (22). We also examined the CHMS data for use of indoor tanning equipment (e.g., beds, booths, and lamps) in the previous 12 months (recorded as "yes" vs. "no") in addition to the frequency (per day/week/month/year) and recent use during the last 2 months.

We assessed other independent variables that are known to be associated with or related to vitD status, melanin level or skin pigmentation, and immigration status. These factors were sex, age, ethnicity, body mass index (BMI, kg/m^2), smoking status, alcohol consumption, age at immigration, length of time in Canada, sun exposure, sunscreen use, season clothing (typically covered or uncovered), physical activity, region and country of birth, ethnicity, intake of vitD-rich foods, use of indoor tanning equipment, and vitD supplements. Details of these factors have previously been described (22).

Study population and CHMS details

We extracted data for 11,579 participants (21.9% immigrants) aged 3–79 years, with a mean (standard error [SE]) age of 39.23 (0.08) years. The study participants were previously defined as healthy (78.3%) and unhealthy (21.7%) in terms of the prevalence of chronic diseases that were diagnosed by healthcare professionals (12). Immigrants had lower concentration levels of S-25(OH)D (mean: 51·23 vs. 62·72; 95% confidence interval [CI]: 8·37, 14·62; $p < 0.001$) compared with non-immigrants (22). Information about the measurement methods, merging of the two data cycles and other CHMS data details are available on the Statistics Canada

website[1] (33, 34), and our previous CHMS-related publications (12, 22).

Statistical analyses

To account for the unequal probability of selection and accurate estimates representing the Canadian population in our analyses, we used the survey command, recommended sample weight, and degrees of freedom. The unweighted results cannot be published (except for correlations) because of Statistics Canada's restrictions policy; therefore, the results are presented as weighted results only.

We used the mean (SE) for comparisons of continuous variables and proportions with 95% CI for categorical variables. Univariate analysis and multivariable linear regression modeling were used to identify factors associated with melanin levels. The models were adjusted for age, sex, immigration status, season, sun exposure, sunscreen use, clothing type, indoor tanning use, smoking, alcohol, physical activity, and travel to sunny climates. Statistical significance was set at $P < 0.05$. We used SPSS version 26.0 (IBM Corp., Armonk, NY, USA) to manage the data and Stata version 16.0 (StataCorp, College Station, TX, USA) to perform the analyses.

Results

The weighted total mean score for skin melanin levels was 16.46 (*SE*: 0.27; 95% CI: 15.90, 17.01). The mean value was higher among immigrants than non-immigrants (17.08 vs. 16.29, $p = 0.004$), but no difference was found between recent (≤10 years) and well-established immigrants (>10 years). Melanin levels were weakly correlated with S-25(OH)D (≥50 nmol/L) ($r = 0.088$; $P < 0.001$). Sex (male), age (≥18 years), BMI (overweight), sun exposure (traveled to sunny climate), sunscreen (non-users), and smoking (currently smoking) were associated with higher melanin levels. The estimated use of indoor tanning beds and lamps among the Canadian population was 5.8% and was higher among non-immigrants than immigrants. The majority (63%) of indoor tanning users reported using tanning beds or lamps every year, and 2% reported at least one session in the last 2 months (data not shown). Melanin was not associated (users: 16.58 *vs*. non-users: 16.51; 95% CI: −0.61, 0.47) or correlated ($r = -0.019$; $p = 0.079$) with the use of tanning equipment or the frequency of use. Moreover, no associations between melanin and clothing type, alcohol consumption, and the level of physical activity were observed (**Table 1**).

People with white ethnicity had less pigmented skin than the non-white population (16.08 vs. 17.56) ($r = 0.243$; $P < 0.001$). Differences in melanin levels between different ethnic groups in the non-white population are presented in **Table 2**.

Those who were born in South and Central America and the Caribbean, Africa, and Asia had higher melanin levels than people from Canada and North America. Differences in melanin were also observed by country of birth; the highest mean level was found among people born in Jamaica and the lowest among those born in Lebanon (**Table 3**).

In the adjusted multivariate linear regression model, factors associated with skin melanin levels were S-25(OH)D, immigration status, sex, age, summer and fall seasons, travel to a sunny climate, sun exposure, sunscreen use, smoking, and alcohol consumption (**Table 4**).

Discussion

This study explored the associations between melanin levels and participants' sociodemographic characteristics and clarified whether melanin levels explained the variations in vitD between immigrants compared with native-born Canadians. Our investigation of melanin levels among immigrants and the association between melanin and S-25(OH)D revealed that immigrants had higher melanin levels (darker skin) compared with non-immigrants, but there was no difference in melanin by their length of stay in Canada. However, melanin had a weak positive correlation with S-25(OH)D levels; this finding contradicted existing knowledge and implied there may be different confounding factors that may interfere with the relationship between melanin levels and vitD in the present cross-sectional observational design. This can be explained also by the fact that although epidemiological studies suggest that melanin inhibits cutaneous vitamin D synthesis by UVB radiation; however, laboratory investigations assessing the impact of melanin on vitamin D production have produced contradictory results. Young et al. found that melanin has a small inhibitory effect on vitamin D synthesis (21). Moreover, in vitiligo where we have a destruction of functional melanocytes it has been found that the application of vitamin D might help in preventing the destruction of melanocytes. This may be through the effect of vitamin D on the intracellular Ca^{+2}, which controls the activity of thioredoxin reductase. The latter is important for thioredoxin, which stimulates tyrosinase activity, the principal enzyme involved in melanin synthesis (35). Therefore, the relationship between melanin serum levels and vitamin D is a bit complicated. We know that exposure to sunlight will lead to darker skin due to increased levels of melanin to protect the skin from the effect of UVB radiation. Meanwhile, for the synthesis of vitamin D, we need to be exposed to sunlight. Hence, sun avoidance may result in decreased melanin levels and also low vitamin D levels. This can explain, at least partially, the positive correlation between melanin and vitamin D levels. This is supported by a study by Glass

1 http://www.statcan.gc.ca, accessed on February 24, 2021.

TABLE 1 Weighted mean melanin levels by S-25(OH)D, immigration, sociodemographic, and lifestyle factors using Canadian Health Measures Survey (CHMS) data (Cycles 3 and 4).

		Mean (SE)	Mean difference (SE)	(95% CI)	*P*-value	*r*	*P*-value
S-25(OH)D (nmol/L)	–	–				0.113	<0.001
S-25(OH)D (nmol/L)	<50†	16.06 (0.28)					
	≥50	16.73 (0.26)	0.68 (0.18)	(0.30, 1.06)	0.001	0.088	<0.001
Immigration status	Non-immigrants†	16.29 (0.29)					
	Immigrants	17.08 (0.25)	−0.78 (0.24)	(−1.29, −0.281)	0.004	0.136	<0.001
Time after immigration (years)	≤10†	17.05 (0.27)					
	>10	17.05 (0.31)	−0.01 (0.32)	(−0.67, 0.65)	0.978	−0.059	0.008
Sex	Male†	17.16 (0.29)	–	–			
	Female	15.75 (0.25)	1.41 (0.12)	(1.16, 1.65)	<0.001	−0.198	<0.001
Age (years)	<18†	16.15 (0.35)					
	≥18	16.52 (0.25)	0.37 (0.14)	(0.07, 0.66)	0.017	0.092	<0.001
BMI (kg/m^2)	Normal weight†	16.40 (0.26)					
	Underweight	16.59 (0.38)	−0.18 (0.29)	(−0.78, 0.42)	0.542	−0.041	0.104
	Overweight	16.75 (0.27)	−0.34 (0.15)	(−0.65, −0.035)	0.031	0.068	<0.001
	Obese	16.17 (0.32)	0.23 (0.18)	(−0.13, 0.60)	0.196	−0.017	0.0751
Sun exposure (min./day)	<30†	16.01 (0.25)					
	≥30	16.51 (0.27)	−0.50 (0.18)	(−0.87, −0.13)	0.010	0.015	0.099
Sunscreen use	No†	17.13 (0.28)					
	Yes	16.21 (0.26)	0.93 (0.12)	(0.67, 1.18)	<0.001	−0.184	<0.001
Traveled to a sunny climate	No†	16.30 (0.28)					
	Yes	17.57 (0.25)	−1.30 (0.16)	(−1.59, −0.92)	<0.001	0.101	<0.001
Tanning equipment	No†	16.51 (0.25)					
	Yes	16.58 (0.37)	−0.07 (0.26)	(−0.61, 0.47)	0.788	−0.019	0.079
Clothing	Uncovered†	16.52 (0.29)					
	Covered	16.41 (0.26)	0.13 (0.14)	(−0.18, 0.34)	0.441	0.017	0.080
Smoking status	Former/never†	16.40 (0.25)					
	Current	16.91 (0.29)	−0.59 (0.16)	(−0.84, −0.17)	0.005	0.063	<0.001
Alcohol consumption	Former/never†	16.65 (0.30)					
	Current	16.47 (0.26)	0.18 (0.20)	(−0.24, 0.60)	0.388	−0.004	0.681
Meet physical activity	No†	16.40 (0.28)					
	Yes	16.55 (0.25)	−0.14 (0.16)	(−0.48, 0.19)	0.384	0.038	0.001

Correlation (*r*) weak or very weak (below ± 0.3). SE, standard error; CI, confidence interval; BMI, body mass index. Significant at $P < 0.05$. †Reference value. The mean S-25(OH)D (nmol/L) for each factor was published in a previous paper (22).

et al. who reported that Caucasian UK females with fair skin types show lower levels of 25(OH)D compared to darker skin types (36).

Previous immigration studies concluded that ethnicity and lifestyle changes, including dietary changes after immigration, along with slow physiological adaptation to the new environment (e.g., lower UV radiation level at the new latitude) mean that immigrants have low levels of S-25(OH)D (13, 19, 24, 37). Moreover, a higher level of skin pigmentation has also been suggested to contribute to lower S-25(OH)D levels (19, 22, 37–39). In the same context, another study found melanin had a slight inhibitory effect on the photosynthesis of

TABLE 2 Weighted mean melanin levels by ethnicity using Canadian Health Measures Survey (CHMS) data (Cycles 3 and 4).

	Mean (SE)	Mean difference (SE)	(95% CI)	*P*-value	*r*	*P*-value
White†	16.08 (0.29)					
Non-white	17.56 (0.25)	−1.54 (0.26)	(−2.07, −1.00)	<0.001	0.243	<0.001
Aboriginal	17.35 (0.44)	−0.93 (0.36)	(−1.67, −0.19)	0.016	0.045	<0.001
South Asian	17.70 (0.41)	−1.62 (0.49)	(−2.63, −0.61)	0.003	0.125	<0.001
Chinese	18.07 (0.60)	−1.99 (0.58)	(−3.18, −0.79)	0.002	0.151	<0.001
Black	19.66 (0.31)	−3.58 (0.40)	(−4.41, −2.74)	<0.001	0.262	<0.001
Filipino	17.06 (0.24)	−0.98 (0.35)	(−1.71, −0.25)	0.010	0.077	<0.001
Latin American	18.25 (0.43)	−2.18 (0.50)	(−3.21, −1.14)	<0.001	0.092	<0.001
Arab	15.88 (0.81)	0.20 (0.81)	(−1.47, 1.87)	0.804	0.033	0.002
Southeast Asian	16.74 (0.76)	−0.65 (0.76)	(−2.23, 0.92)	0.397	0.004	0.716
West Asian	16.26 (0.58)	−0.17 (0.63)	(−1.49, 1.13)	0.781	0.039	0.004
Korean	15.03 (1.70)	1.05 (1.70)	(−2.49, 4.58)	0.545	0.021	0.376
Japanese	16.41 (0.90)	−0.33 (0.93)	(−2.26, 1.60)	0.724	0.011	0.294
Multiple ethnicities	16.84 (0.39)	−1.70 (0.89)	(−1.50, −0.13)	0.046	0.105	<0.001
Other ethnicities	17.78 (0.99)	−0.76 (0.36)	(−3.56, 0.15)	0.070	0.064	<0.001

Correlation (*r*) weak or very weak (below ± 0.3). SE, standard error; CI, confidence interval. Significant at $P < 0.05$. †Reference value. The mean S-25(OH)D (nmol/L) for each ethnicity was published in a previous paper (22).

vitD3 among healthy participants who had skin types II–VI (white to black) (21).

Evidence from immigration studies on acculturation and vitD found the length of time since immigration was a crucial indicator of lifestyle adaptation. Immigrants, over time, tailored to the lifestyle of the host country. The higher adaptation levels were associated with higher S-25(OH)D levels (22, 40, 41). Moreover, the length of stay in the host country was also associated with the lightening of skin color as part of the genomic adaptation process (42). However, we found no differences in skin melanin levels between recent and well-established immigrants. Similarly, we found a weak negative correlation between skin melanin and longer residency duration in Canada, which may be explained by the slight lightening of skin over time due to slow genomic adaptation (42).

In our previous related publication (22), the multivariate analysis showed that the S-25(OH)D level was found positively associated with age [Beta Estimate (SE) 0.14 (0.04)]. The lowest S-25(OH)D levels were found among the youth aged 12–17 years. Few studies have sought to define the difference in melanin levels/skin pigmentation in terms of sociodemographic (e.g., sex, age, and BMI) and behavioral variations (e.g., smoking, physical activity, and indoor tanning), and no available studies have considered immigrants' country of birth or ethnicity (43–45).

Consistent with our finding of higher melanin levels among males and older people, a previous study reported a higher melanin index among men compared with women and among people aged 20–30 years compared with those aged 10–20 years (44). Lighter skin among older people was reported to be caused by a decrease in the number of melanocytes, which is estimated to decrease by around 8–20% per decade (46). Our findings of higher melanin levels among non-sunscreen users, those who were exposed to the sun (including traveling to sunny climates), and current smokers were consistent with previously published research (21, 43, 44, 47, 48).

The significantly higher melanin levels among overweight people compared with those with normal body weight noted in this study were consistent with the involvement of melanin in the expression of components of the melanogenic pathway in the adipocytes. A previous study found that relative to lean people, the adipose tissue of obese patients had higher amounts of melanin, which is known for its antioxidant and anti-inflammatory properties that help in scavenging reactive oxygen species and suppress oxidative stress and inflammation in adipocytes (45).

Indoor tanning use is increasing and becoming a widespread industry that is now more accessible to the public. Tanning machines emit UV light, which can theoretically increase S-25(OH)D levels. However, the Endocrine Society reported that tanning caused darkening of the skin by increasing melanin production, which aims to protect the skin against the damaging effect of UV radiation; this high melanin production limits the ability of the skin to synthesize more vitD (49). However, we found that only 2% of the CHMS participants reported indoor tanning in the last 2 months, and the use of tanning

TABLE 3 Weighted mean melanin levels by geographical region and country of birth using Canadian Health Measures Survey (CHMS) data (Cycles 3 and 4).

		Mean (SE)	Mean difference (SE)	(95% CI)	*P*-value	*r*	*P*-value
Region of birth	Canada and North America†	16.28 (0.30)	–	–	–		
	South and Central America and the Caribbean	18.80 (0.31)	−2.52 (0.35)	(−3.26, −1.79)	<0.001	0.121	<0.001
	Europe	16.29 (0.33)	−0.01 (0.29)	(−0.62, 0.59)	0.971	0.023	0.024
	Africa	17.44 (0.76)	−1.16 (0.73)	(−2.68, 0.36)	0.127	0.088	<0.001
	Asia	17.10 (0.26)	−0.81 (0.1)	(−1.45, −0.18)	<0.014	0.112	<0.001
Country of birth	Canada†	16.28 (0.30)	–	–	–		
	China	16.58 (0.43)	−0.30 (0.49)	(−1.3, 0.72)	0.546	0.021	0.040
	USA	16.03 (0.41)	0.24 (0.42)	(−0.62, 1.12)	0.560	0.005	0.619
	France	16.34 (0.92)	−0.06 0(0.86)	(−1.86, 1.74)	0.946	−0.006	0.564
	Jamaica	20.32 (0.49)	−4.04 (0.45)	(−4.98, −3.10)	<0.001	0.077	<0.001
	UK	16.72 (0.67)	−0.44 (0.67)	(−1.84, 0.95)	0.517	0.008	0.408
	Algeria	15.31 (1.48)	0.97 (1.43)	(−2.00, 3.95)	0.504	−0.010	0.328
	Mexico	18.16 (1.28)	−1.88 (1.27)	(−4.53, 0.77)	0.156	0.023	0.027
	Pakistan	17.79 (0.79)	−1.51 (0.73)	(−3.04, 0.02)	0.052	0.048	<0.001
	Netherlands	16.60 (0.52)	−0.32 (0.51)	(−1.37, 0.73)	0.534	0.017	0.100
	India	18.62 (0.34)	−2.33 (0.40)	(−3.18, −1.50)	<0.001	0.113	<0.001
	Philippines	16.91 (0.22)	−0.63 (0.36)	(−1.38, 0.13)	0.101	0.050	<0.001
	Romania	16.86 (1.10)	−0.58 (1.10)	(−2.85, 1.70)	0.604	0.003	0.798
	Hong Kong	16.25 (0.55)	0.03 (0.66)	(−1.33, 1.40)	0.960	−0.003	0.743
	Germany	16.78 (1.12)	−0.51 (1.10)	(−2.77, 1.75)	0.443	0.024	0.046
	Colombia	16.90 (0.84)	−0.62 (0.96)	(−2.60, 1.37)	0.525	0.033	0.002
	Morocco	16.35 (1.68)	−0.07 (1.66)	(−3.51, 3.37)	0.968	0.011	0.270
	Italy	15.59 (0.80)	0.69 (0.75)	(−0.88, 2.25)	0.371	0.004	0.722
	Iran	16.37 (0.30)	−0.09 (−0.86)	(−1.86, 1.69)	0.920	0.020	0.049
	Lebanon	15.40 (0.28)	0.88 (0.36)	(0.13, 0.6)	0.023	−0.004	0.691
	Other	17.08 (0.26)	−0.80 (0.28)	(−1.39, −0.21)	0.010	0.125	<0.001
	All (153 countries)	16.99 (0.23)	0.71 (0.24)	(−1.22, −0.21)	0.008	0.138	<0.001

Correlation (*r*) weak or very weak (below ± 0.3). SE, standard error; CI, confidence interval. Significant at $P < 0.05$. †Reference value. The mean S-25(OH)D (nmol/L) for each region\country of birth was published in a previous paper (22).

equipment did not significantly impact skin melanin levels, although this may be affected by the frequency and duration of tanning equipment use. Moreover, knowledge about melanin synthesis, migration to the skin, degradation, and the impact on S-25(OH)D concentration is not well-established (50). Therefore, other confounding factors may impact the effect of tanning UV exposure among immigrants (darker skin) and non-immigrants (lighter skin).

The notable variation in melanin levels among immigrants from different ethnicities and origins in this study could be explained by genetic and epigenetic (potential genetic changes that affect gene expression without involving changes in the original sequence of DNA nucleotides) variations in melanogenesis (51). Melanogenesis is a complex process in which melanin is synthesized in melanocytes and transported to keratinocytes. This process involves multiple signaling pathways and genes (48).

An important factor that helps to understand variations in S-25(OH)D levels in response to skin melanin levels is skin type. Different skin types (e.g., Fitzpatrick skin type [FST] I–VI) have

TABLE 4 Multivariable linear regression analysis based on melanin and immigration status using Cycles 3 and 4 of Canadian Health Measures Survey (CHMS) data.

	Melanin level		
	Beta estimate (SE)	(95% CI)	*P*-value
S-25(OH)D (nmol/L)	0.01 (0.004)	(0.001, 0.02)	0.039
Immigration status (immigrant)	0.62 (0.21)	(0.17, 1.06)	0.009
Sex (female)	−1.64 (0.14)	(−1.92, −1.35)	<0.001
Age	0.02 (0.004)	(0.01, 0.03)	<0.001
Season (summer)	2.69 (0.42)	(1.80, 3.57)	<0.001
Season (fall)	1.75 (0.43)	(0.84, 2.65)	0.001
Sun exposure (yes)	0.48 (0.19)	(0.09, 0.87)	0.017
Traveled to a sunny climate (yes)	1.44 (0.19)	(1.04, 1.84)	<0.001
Sunscreen use (yes)	−0.45 (0.13)	(−0.73, −0.18)	0.002
Smoking (current)	0.67 (0.16)	(0.28, 0.94)	0.001
Alcohol (current)	−0.52 (0.16)	(−0.84, −0.19)	0.003
Const.	14.45 (0.73)	(12.93, 15.98)	<0.001

Linear regression adjusted for immigration status, S-25(OH)D, age, sex, season, sun exposure, sunscreen use, clothing, tanning, smoking, alcohol, physical activity, and travel to a sunny country. SE, standard error; CI, confidence interval. Significant at $P < 0.05$.

been shown to behave differently in response to exposure to UV radiation; therefore, the inhibitory effect of skin melanin on vitD synthesis varies (52). Recent work by Young et al. revealed that skin type II was significantly steeper than the other groups in relation to vitD levels after exposure to UV radiation, and a comparison between extreme skin types (II and VI) showed melanin inhibition factors of approximately 1.3–1.4 (21).

The present study is a continuation of our previous work (12, 13, 22), which revealed that ethnicity and sociodemographic factors were the factors most strongly associated with S-25(OH)D. Japanese, Arabs, and Southeast Asians were found to have the lowest S-25(OH)D levels and the most deficient ethnic groups compared with the white group (22). Demonstrating robust associations between these factors and both skin melanin and serum vitD levels reinforces the value of considering the role of ethnicity and various sociodemographic factors when designing national intervention programs to improve vitD status.

In addition to offering national and representative data, the strengths of the CHMS include the study design and large sample size that captured the ethnocultural diversity of immigrants from more than 150 countries and over 13 major ethnic groups. Moreover, melanin level based on the DSM II ColorMeter method is a reliable indication of skin pigmentation. The DSM II ColorMeter method had similar diagnostic characteristics to FST for discerning vitD deficiency and therefore offers an inexpensive, useful surrogate measure of skin color in vitD research (28, 29). However, both methods have been criticized for their limitations in skin classification and imprecisely measuring skin color and reflecting melanin levels (29). Based on a recent systematic review and meta-analysis of reliable tools for assessing skin color (29), we recommend further research uses more reliable tools. In addition, further studies are warranted to elucidate the precise genetics underpinning skin color adaptation and the genetic architecture of skin color adaptation in different ethnic groups. Developing this knowledge will help to address gaps in the literature. An important limitation of our study was that we could not infer causality because of the cross-sectional observational design.

Conclusion

Skin melanin levels appeared to be associated with several sociodemographic and behavioral characteristics. First-generation immigrants had higher melanin levels (darker skin) than non-immigrants, but there was no difference in melanin related to their length of stay in Canada. The weak positive correlation between melanin and S-25(OH)D levels in this study suggested the involvement of various environmental (e.g., dietary and behavioral) confounders and genetic factors that may interfere with the relationships between melanin level, vitD, and immigration status.

Data availability statement

The datasets presented in this manuscript, codebook, and analytic code cannot be made public as they are confidential and hosted by Statistics Canada. Further queries may be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the secondary data analysis of the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SY and GW conceived the study. With close supervision from GW, SY managed the data, verified the analytical methods,

and prepared the tables. AH verified the underlying data at the Research Data Center. SY, MF, and HH interpreted the results. SY prepared the final draft. All authors contributed to the design and analysis of the research and substantive review of the manuscript and approved the submitted version.

Funding

CHMS data were obtained and supported by funding to the Canadian Research Data Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors acknowledge the Carleton, Ottawa, Outaouais Local Research Data Center team for assistance with access to CHMS data.

Conflict of interest

MP was employed by Eli Lilly Canada Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author disclaimer

This research and analyses were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

References

1. Boissy RE. Melanosome transfer to and translocation in the keratinocyte. *Exp Dermatol.* (2003) 12:5–12. doi: 10.1034/j.1600-0625.12.s2.1.x

2. Mapunya MB, Lall N. Melanin and its role in hyper-pigmentation–current knowledge and future trends in research. In: Tanaka Y editor. *Breakthroughs in Melanoma Research*. London: IntechOpen (2011).

3. Markiewicz E, Idowu OC. Melanogenic difference consideration in ethnic skin type: a balance approach between skin brightening applications and beneficial sun exposure. *Clin Cosmet Investig Dermatol.* (2020) 13:215. doi: 10.2147/CCID.S245043

4. Schlessinger DI, Anoruo M, Schlessinger J. *Biochemistry, Melanin*. Tampa, FL: StatPearls Publishing (2021).

5. Xu C, Chen T, Li J, Jin M, Ye M. The structural analysis and its hepatoprotective activity of melanin isolated from Lachnum sp. *Process Biochem.* (2020) 90:249–56. doi: 10.1016/j.procbio.2019.08.022

6. Hung Y, Sava V, Blagodarsky V, Hong M-Y, Huang G. Protection of tea melanin on hydrazine-induced liver injury. *Life Sci.* (2003) 72:1061–71. doi: 10.1016/S0024-3205(02)02348-2

7. Mohagheghpour N, Waleh N, Garger SJ, Dousman L, Grill LK, Tusé D. Synthetic melanin suppresses production of proinflammatory cytokines. *Cell Immunol.* (2000) 199:25–36. doi: 10.1006/cimm.1999.1599

8. Torequl Islam M, Salehi B, Karampelas O, Sharifi-rad J, Oana Docea A, Martorell M, et al. High skin melanin content, vitamin d deficiency and immunity: potential interference for severity of COVID-19. *Farmacia.* (2020) 68:970–83. doi: 10.31925/farmacia.2020.6.3

9. Renzaho AMN, Halliday Bhsci JA, Nowson C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review. *Nutrition.* (2011) 27:868–79. doi: 10.1016/j.nut.2010.12.014

10. Peterlik M, Boonen S, Cross HS, Lamberg-Allardt C. Vitamin D and calcium insufficiency-related chronic diseases: an emerging world-wide public health problem. *Int J Environ Res Public Health.* (2009) 6:2585–607. doi: 10.3390/ijerph6102585

11. Ghasemian R, Shamshirian A, Heydari K, Malekan M, Alizadeh-Navaei R, Ebrahimzadeh MA, et al. The role of vitamin D in the age of COVID-19: a systematic review and meta-analysis. *Int J Clin Pract.* (2020) 75:e14675. doi: 10.1111/ijcp.14675

12. Yousef S, Colman I, Papadimitropoulos M, Manuel D, Hossain A, Faris M, et al. Vitamin D and chronic diseases among first-generation immigrants: a large-scale study using Canadian health measures survey (CHMS) data. *Nutrients.* (2022) 14:1760. doi: 10.3390/nu14091760

13. Yousef S, Elliott J, Manuel D, Colman I, Papadimitropoulos M, Hossain A, et al. Study protocol: worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - A systematic review and meta-analysis. *Syst Rev.* (2019) 8:211. doi: 10.1186/s13643-019-1123-4

14. Umar M, Sastry KS, Chouchane AI. Role of vitamin D beyond the skeletal function: a review of the molecular and clinical studies. *Int J Mol Sci.* (2018) 19:1618. doi: 10.3390/ijms19061618

15. Amanzholkyzy A, Nurgalieva RE, Dosimov AZ, Stankevicius E, Kaldybaeva AT. Ethnic manifestations of gene polymorphisms of vitamin D receptor (VDR) in adolescents of Western Kazakhstan Region. *J Natl Med Assoc.* (2018) 110:78–83. doi: 10.1016/j.jnma.2017.02.012

16. Jablonski NG, Chaplin G. Human skin pigmentation, migration and disease susceptibility. *Philos Trans R Soc B Biol Sci.* (2012) 367:785–92. doi: 10.1098/rstb.2011.0308

17. Carlberg C. *Vitamin D and Pigmented Skin*. Basel: Multidisciplinary Digital Publishing Institute (2022). 325 p. doi: 10.3390/nu14020325

18. Ito S, Wakamatsu K. Quantitative analysis of eumelanin and pheomelanin in humans, mice, and other animals: a comparative review. *Pigment Cell Res.* (2003) 16:523–31. doi: 10.1034/j.1600-0749.2003.00072.x

19. Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region

of birth: a meta-analysis. *Nutrition.* (2016) 32:21–32. doi: 10.1016/j.nut.2015.07.007

20. Spiro A, Buttriss JL. Vitamin D: an overview of vitamin D status and intake in Europe. *Nutr Bull.* (2014) 39:322–50. doi: 10.1111/nbu.12108

21. Young AR, Morgan KA, Ho T-W, Ojimba N, Harrison GI, Lawrence KP, et al. Melanin has a small inhibitory effect on cutaneous vitamin D synthesis: a comparison of extreme phenotypes. *J Investig Dermatol.* (2020) 140:1418–26.e1. doi: 10.1016/j.jid.2019.11.019

22. Yousef S, Manuel D, Colman I, Papadimitropoulos M, Hossain A, Faris M, et al. Vitamin D status among first-generation immigrants from different ethnic groups and origins: an observational study using the Canadian health measures survey. *Nutrients.* (2021) 13:2702. doi: 10.3390/nu13082702

23. Statistics Canada. *Population Projections for Canada, provinces and Territories*. Ottawa, ON: Statistics Canada (2014).

24. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. *Global Vitamin D Status and Determinants of Hypovitaminosis D*. London: Osteoporosis International Springer (2009). p. 1807–20. doi: 10.1007/s00198-009-0954-6

25. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Bull World Health Organ.* (2007) 85:867–72. doi: 10.2471/BLT.07.045120

26. Day B, Langlois R, Tremblay M, Knoppers B-M. Canadian health measures survey: ethical, legal and social issues. *Health Rep.* (2007) 18:37–51.

27. Ng E. Canadian health measures survey: a tool for immigrant health research? *Health Rep.* (2015) 26:3–9.

28. Khalid AT, Moore CG, Hall C, Olabopo F, Rozario NL, Holick MF, et al. Utility of sun-reactive skin typing and melanin index for discerning vitamin D deficiency. *Pediatr Res.* (2017) 82:444–51. doi: 10.1038/pr.2017.114

29. Langeveld M, van de Lande LS, O'Sullivan E, van der Lei B, van Dongen JA. Skin measurement devices to assess skin quality: a systematic review on reliability and validity. *Skin Res Technol.* (2022) 28:212–24. doi: 10.1111/srt.13113

30. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. *Dietary Reference Intakes Calcium Vitamin D Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board2011*. Washington, DC: National Academies Press (2011).

31. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Pract Res Clin Endocrinol Metabol.* (2011) 25:681–91. doi: 10.1016/j.beem.2011.06.009

32. Dawson-Hughes B. *Vitamin D Deficiency in Adults: Definition, Clinical Manifestations, and Treatment - UpToDate*. (2021). Available online at: https://www.uptodate.com/contents/vitamin-d-deficiency-in-adults-definition-clinical-manifestations-and-treatment (accessed September 6, 2022).

33. Statistics Canada. *Canadian Health Measures Survey, Cycle 4, 2014-2015 - Privacy Impact Assessment Summary*. Ottawa, ON: Statistics Canada (2021).

34. Statistics Canada. *Canadian Health Measures Survey, Cycle 3, Privacy Impact Assessment 2012-2013*. (2021). Available online at: https://www.statcan.gc.ca/eng/about/pia/chmsc3 (accessed March 15, 2021)

35. Oikawa A, Nakayasu M. Stimulation of melanogenesis in cultured melanoma cells by calciferols. *FEBS Lett.* (1974) 42:32–5. doi: 10.1016/0014-5793(74)80272-3

36. Glass D, Lens M, Swaminathan R, Spector TD, Bataille V. Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK. *PLoS One.* (2009) 4:e6477. doi: 10.1371/journal.pone.0006477

37. Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr.* (2016) 103:1033–44. doi: 10.3945/ajcn.115.120873

38. Nimitphong H, Holick MF. Prevalence of Vitamin D Deficiency in Asia Vitamin D status and sun exposure in Southeast Asia. *Dermato Endocrinol.* (2013) 5:34–7. doi: 10.4161/derm.24054

39. Bonilla C, Ness AR, Wills AK, Lawlor DA, Lewis SJ, Davey Smith G. Skin pigmentation, sun exposure and vitamin D levels in children of the Avon Longitudinal Study of Parents and Children. *BMC Public Health.* (2014) 14:597. doi: 10.1186/1471-2458-14-597

40. Sanou D, O'Reilly E, Ngnie-Teta I, Malek Batal, Mondain N, Andrew C, et al. Acculturation and nutritional health of immigrants in Canada: a scoping review. *J Immigrant Minority Health.* (2014) 16:24–34. doi: 10.1007/s10903-013-9823-7

41. Salant T, Diane SL. Measuring culture: a critical review of acculturation and health in Asian immigrant populations. *Soc Sci Med.* (2003) 71:71–90. doi: 10.1016/S0277-9536(02)00300-3

42. Carlberg C. Nutrigenomics of vitamin D. *Nutrients.* (2019) 11:676. doi: 10.3390/nu11030676

43. Haresaku S, Hanioka T, Tsutsui A, Watanabe T. Association of lip pigmentation with smoking and gingival melanin pigmentation. *Oral Dis.* (2007) 13:71–6. doi: 10.1111/j.1601-0825.2006.01249.x

44. Firooz A, Sadr B, Babakoohi S, Sarraf-Yazdy M, Fanian F, Kazerouni-Timsar A, et al. Variation of biophysical parameters of the skin with age, gender, and body region. *Sci World J.* (2012) 2012:386936. doi: 10.1100/2012/386936

45. Page S, Chandhoke V, Baranova A. Melanin and melanogenesis in adipose tissue: possible mechanisms for abating oxidative stress and inflammation? *Obesity Rev.* (2011) 12:e21–31. doi: 10.1111/j.1467-789X.2010.00773.x

46. Costin G-E, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB J.* (2007) 21:976–94. doi: 10.1096/fj.06-6649rev

47. Cho YH, Jeong DW, Seo SH, Lee SY, Choi EJ, Kim YJ, et al. Changes in skin color after smoking cessation. *Korean J Family Med.* (2012) 33:105. doi: 10.4082/kjfm.2012.33.2.105

48. Solano F. Photoprotection versus photodamage: updating an old but still unsolved controversy about melanin. *Polymer Int.* (2016) 65:1276–87. doi: 10.1002/pi.5117

49. The Endocrine Society. *Tanning may Protect Skin against Harmful UV Irradiation but Block Vitamin D Synthesis ScienceDaily*. Washington, DC: The Endocrine Society. (2016).

50. Pham T. *Vitamin D Status of Immigrant and Ethnic Minority children Ages 2 to 5 y in Montréal*. Montreal, QC: McGill University (2012).

51. Zhou S, Zeng H, Huang J, Lei L, Tong X, Li S, et al. Epigenetic regulation of melanogenesis. *Ageing Res Rev.* (2021) 69:101349. doi: 10.1016/j.arr.2021.101349

52. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol.* (1988) 124:869–71. doi: 10.1001/archderm.124.6.869

nutrients

MDPI

Article

Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data

Said Yousef [1,2,*], Ian Colman [1], Manny Papadimitropoulos [3,4], Douglas Manuel [5,6,7], Alomgir Hossain [1,6], MoezAlIslam Faris [8] and George A. Wells [1,2]

1 Faculty of Medicine, School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON K1G 5Z3, Canada; icolman@uottawa.ca (I.C.); alhossain@ottawaheart.ca (A.H.); gawells@ottawaheart.ca (G.A.W.)
2 Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON K1Y 4W7, Canada
3 Eli Lilly Canada Inc., Toronto, ON M5X 1B1, Canada; papadimitropoulos_manny@lilly.com
4 Faculty of Pharmacy, University of Toronto, Toronto, ON M5S 3M2, Canada
5 Ottawa Hospital Research Institute, Ottawa, ON K1Y 4E9, Canada; dmanuel@ohri.ca
6 Institute for Clinical Evaluative Sciences, Ottawa, ON K1Y 4E9, Canada
7 Department of Family Medicine, University of Ottawa, Ottawa, ON K1H 8M5, Canada
8 Department of Clinical Nutrition and Dietetics, Research Institute of Medical and Health Sciences (RIMHS), College of Health Sciences, University of Sharjah, Sharjah 27272, United Arab Emirates; mfaris@sharjah.ac.ae
* Correspondence: Said Yousef

Abstract: Background: Nearly 22% of the Canadian population are first-generation immigrants. We investigated immigrants' health status and health deterioration over time in terms of the prevalence of chronic diseases (CDs) and their relationship to vitD status. **Methods:** We used cycles three (2012–2013) and four (2014–2015) of the Canadian Health Measures Survey. These data contained unique health information and direct physical/blood measures, including serum 25-hydroxyvitamin D (S-25(OH)D). Indicators of health status and deterioration were the prevalence of CDs diagnosed by healthcare professionals, self-reported general and mental health, and CD-related biomarkers. **Results:** The data (n = 11,579) included immigrants from more than 153 countries. Immigrants were healthier than non-immigrants for most health status measures. The prevalence of CDs was higher among those who migrated to Canada aged $\geq$ 18 years. A longer time in Canada after immigration was associated with a higher risk for CDs. The mean S-25(OH)D was lower among immigrants, higher among patients with CDs, and inversely associated with glycated hemoglobin, total cholesterol/high-density lipoprotein ratio, immunoglobulin E, serum ferritin, and blood hemoglobin. After adjusting for covariates, no association was found between S-25(OH)D and the prevalence of CDs. **Conclusions:** Lower levels of accumulated S-25(OH)D among immigrants may impact their health profile in terms of CD-related biomarkers, which partially explains immigrants' health deterioration over time. We recommend further longitudinal research to investigate immigrants' vitD and health deterioration.

Keywords: immigrants' health deterioration; vitamin D; serum 25-hydroxyvitamin D; chronic diseases

check for updates

Citation: Yousef, S.; Colman, I.; Papadimitropoulos, M.; Manuel, D.; Hossain, A.; Faris, M.; Wells, G.A. Vitamin D and Chronic Diseases among First-Generation Immigrants: A Large-Scale Study Using Canadian Health Measures Survey (CHMS) Data. *Nutrients* **2022**, *14*, 1760. https://doi.org/10.3390/nu14091760

Academic Editor: Tyler Barker

Received: 16 March 2022
Accepted: 18 April 2022
Published: 22 April 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Immigrants are a fundamental part of the Canadian population and policy framework [1], with nearly 22% of the Canadian population being first-generation immigrants [2]. Statistics Canada estimated an increase of approximately 1 million foreign-born residents every 3 years by 2035/2036 [3]. Therefore, the health of immigrants will impact Canada's overall future healthcare system.

Accumulated evidence suggests that recent immigrants have better health than people of the host country, including long-term immigrants who had previously migrated to

the host country. This phenomenon is called the "healthy immigrant effect" or "healthy immigrant advantage" [4–6]. However, immigrants' physical and mental health declines after arrival in Canada, with health changes often occurring within 5–10 years [4,5]. Pre-migration factors, such as rigorous selection criteria that favor immigrants that are healthier, wealthier, and better educated, along with post-immigration factors, such as environmental and lifestyle changes, may explain this health decline after migration [4,7–10]. In addition, the healthy immigrant effect varies through the course of life [6].

Moreover, more immigrants have deficient and insufficient vitamin D (vitD) levels compared with native-born populations [2,11,12]. However, vitD status varies among immigrants because of ethnic variations, skin pigmentation, resettlement changes in diet, physical activity, and sun exposure [2,11,13,14]. The concentration of serum 25-hydroxyvitamin D (S-25(OH)D) represents the combined contributions of the cutaneous synthesis and dietary intake of vitD and is considered the most important clinical marker for the overall vitD level [12,15,16]. A lower concentration of S-25(OH)D was found to be a risk factor for CDs [17–20] and could predict all-cause mortality [17,18,21]. Moreover, Jablonski et al. expected the diseases associated with vitD deficiency to be a major source of morbidity and mortality in the 21st century [22]. Most recent guidelines have emphasized the importance of vitD for skeletal health, although evidence supporting its benefits for non-skeletal health outcomes is either weak or conflicting [23,24]. There is a range of recommended vitD thresholds that are used to study health effects. Mean S-25(OH)D (nmol/L) values or ranges at various thresholds (e.g., deficiency: 25–30 nmol/L; insufficiency: 25–49 nmol/L; and sufficiency: 50–75 nmol/L) are commonly used in studies to describe vitD status [12]. An insufficient vitD level (<50 nmol/L) is more frequently used to describe hypovitaminosis D [25].

vitD deficiency has been linked to physical and mental illnesses [26,27]. Recent research supported the hypothesis that vitD deficiency was related to the incidence, severity [28,29], and mortality attributed to COVID-19 [29,30]. These studies concluded that those at the highest risk for severe COVID-19 matched those at the highest risk for severe vitD deficiency, including older people, darker-skinned ethnic groups, and obese people [28,30,31]. Moreover, research has highlighted the importance of further studies investigating immigrants' health deterioration in the context of vitD [2,32], lifelong adversity [33], and changes in lifestyle and dietary intake [5,32]. However, leading causes of death, such as CDs (cardiovascular disease, cancer, chronic lung disease, and diabetes), are used as reliable measures for public health [34].

The main objective of this study was to investigate immigrants' health status and possible health deterioration in relation to serum vitD levels. Moreover, we used CDs and CD-related biomarkers as proxy indicators to investigate risk factors for health deterioration in the context of vitD status. In addition, we compared the health status (in relation to the vitD status) of immigrants from different ethnic groups and origins with non-immigrants.

2. Materials and Methods

2.1. Study Design and Participants

We previously published the main characteristics, mean S-25(OH)D levels, and prevalence and leading determinants of vitD deficiency/insufficiency among immigrants and non-immigrants in Canada [2]. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement in the planning, implementation, and reporting [35].

Health and vitD status among first-generation immigrants (foreign-born) were ascertained using Canadian Health Measures Survey (CHMS) data and compared with those in the non-immigrant (native-born) population. The CHMS represents the first national data on vitD, includes the Canadian immigrant population, addresses gaps in existing national information, and contains unique health information, including direct physical and blood measures [36,37]. The sample size for each CHMS cycle was carefully selected to provide a reliable and representative estimate at the national level for sex and age groups. The

survey covered approximately 96% of the Canadian population. A dwelling stratification stage was applied, followed by a roster list of all people living in each household, from which individuals aged 3–79 years were randomly selected [36,37]. The CHMS sample population weight was adjusted for age and sex across Canada's five standard geographic regions. All participants provided written informed consent, and the CHMS was approved by the Health Canada Research Ethics Board [36,37].

2.2. Measures

The S-25(OH)D is expressed in nanomoles per liter (nmol/L) and is measured using chemiluminescence immunoassay technology (DiaSorin®, Ltd., Stillwater, MN, USA). The analytical detection limit for S-25(OH)D was 10–375 nmol/L. We used S-25(OH)D cut-off points to identify vitD status as either sufficient (≥50 nmol/L) or insufficient (<50 nmol/L), as defined by the Institute of Medicine (IOM) and other experts [12,38,39].

We used the presence of CDs as the outcome-dependent factor for health deterioration. CDs included 24 chronic diseases and conditions (e.g., type 1 and 2 diabetes, heart disease (not limited to ischemic heart disease), and mood disorder). Respondents were asked "Do you have a long-term condition that was diagnosed by a healthcare professional and expected to last or has already lasted 6 months or more?" (yes/no). We used CDs (e.g., diabetes, heart disease, cancer, and asthma) for which a date of diagnosis was listed. We combined CDs that had similar inflammatory characteristics (including, but not limited to chronic obstructive pulmonary disease, bronchitis, and emphysema) as one variable called "inflammatory lung diseases." Inflammatory lung diseases were measured for participants aged > 29 years, but no date of diagnosis was available. CDs were considered present if at least one of the five listed health conditions (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases) received a "yes" response as a separate variable called "CDs". The date of diagnosis for the CDs was not available.

Our analysis examined: five health conditions (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases), CDs (at least one), self-rated general health, and self-rated mental health. We also considered seven biomarkers associated with CDs: glycated hemoglobin (HbA1c), the total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL ratio), high-sensitivity C-reactive protein (hs-CRP), immunoglobulin E (IgE), ferritin, hemoglobin (Hb), and S-25(OH)D (the serum concentration of vitD). In addition, 16 sociodemographic and health behavior variables were examined as independent factors: immigration status, sex, age, income, education level, body mass index (BMI; kg/m^2), smoking status, alcohol consumption, age at immigration, length of time in Canada, physical activity, region, country of birth, ethnicity, dairy intake, and vitD supplement use.

The CHMS was a cross-sectional survey. Data for health measures, including several temporal attributes such as date of immigration and mobile clinic visit dates (e.g., blood sampling including S-25(OH)D), were used to create proxy health indicators for health deterioration. To examine longitudinal changes in health, we created a new variable to compare "diagnosis before immigration" versus "diagnosis after immigration". We also created a new variable "time after diagnosis" to investigate the relationship between S-25(OH)D and the presence of CDs. We used two categories (recent vs. long-term) for diagnosis at two time-points (1 year and 5 years). We used the lowest cut-off value to represent the most recent S-25(OH)D measures at the date of diagnosis (e.g., ≤1 year and ≤5 years) and the highest to represent the long-term measures for S-25(OH)D at the date of diagnosis (e.g., >1 year and >5 years).

A Likert scale was used for the two self-reported questions that reflected the quality of general and mental health. Participants aged over 12 years rated these questions, with the ratings for each question dichotomized in two categories: "fair/poor" versus "good" (excellent/very good/good).

Detailed information about the CHMS data, methods, and merging of the two cycles can be found in our previous work [2] and on the Statistics Canada website (http://www.

statcan.gc.ca, accessed 14 February 2021) [40,41]. The method of measurement and the analytical detection limit for each biomarker are available in Appendix A, Table A1.

2.3. Statistical Analysis

Following the recommendations of Statistics Canada, all analyses used population weights that reflected the probability a respondent was included in the survey. Descriptive statistics were used to investigate immigrants' demographic, clinical, and behavioral characteristics compared with non-immigrants. We used the mean and standard error (SE) for continuous variables. Data were stratified based on the study outcomes (CDs) and variables of interest (e.g., immigration status). To account for the unequal probability of selection and present an accurate estimate of the Canadian population, we used the survey command, recommended sample weight, and degrees of freedom in the analyses. Therefore, all results were weighted values. In addition to the two S-25(OH)D cutoff points (sufficient $\geq$ 50 nmol/L and insufficient < 50 nmol/L), we used the continuous values for S-25(OH)D and other biomarkers.

We used univariate analyses to identify independent covariates. Multivariable logistic regression models (odds ratio (OR) and 95% confidence interval (CI)) were then used to evaluate the association between CDs (indication of health deterioration) and vitD status for immigrants compared with non-immigrants. The final model was adjusted for immigration status, age, sex, household income, education, ethnicity, BMI, physical activity, smoking behavior, alcohol consumption, vitD supplement use, HbA1c, the TC/HDL ratio, Hb, ferritin, IgE, and hs-CRP. Statistical significance was set at $p \leq 0.05$. All analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and Stata version 16.0 (StataCorp, College Station, TX, USA).

3. Results

We examined data for 11,579 CHMS participants, including immigrants from more than 153 countries. The main characteristics of the study sample have previously been published [2]. The prevalence rates of CDs based on the sociodemographic and immigration characteristics of all study participants are presented in Table 1. Immigrants had a lower prevalence of CDs than non-immigrants. Those who had migrated to Canada at age $\geq$ 18 years had a higher prevalence of CDs than those who migrated at under 18 years of age. At two different time points after the migration (5 and 10 years), the prevalence was higher among those who had stayed in Canada for $\geq$5 years and $\geq$10 years than among those who had stayed less than 5/10 years. The prevalence of CDs was higher among immigrants with older age, lower household income, underweight, overweight, and obesity compared with their younger, higher income, and average body weight counterparts. Participants who did not meet the Canadian physical activity recommendations had a higher prevalence of CDs.

Table 1. Weighted prevalence of chronic diseases by sociodemographic and behavioral characteristics and immigration status.

		No CDs † **(78.3%), %**	**CDs (21.7%), %**	***p*-Value**
Immigration status	Non-immigrant †	76.80	23.20	<0.001
	Immigrant	83.36	16.64	
Age at immigration, years	<18 years †	91.69	8.31	<0.001
	≥18	74.75	25.25	
Years after immigration	≤5 years †	91.72	8.28	0.004
	>5	80.98	19.02	

Table 1. *Cont.*

		No CDs † (78.3%), %	CDs (21.7%), %	*p*-Value
Years after immigration	≤10 years †	92.84	7.16	<0.001
	>10	77.34	22.66	
Sex	Male †	78.67	21.33	0.641
	Female	77.88	22.12	
Age group, years	<5	92.92	7.08	<0.001
	5–11	89.83	10.17	
	12–17	85.14	14.86	
	18–64 †	80.01	19.99	
	>64	52.7	47.3	
Household income (CAD)	<50,000	72.34	27.66	<0.001
	50,000–100,000 †	80.35	19.65	
	>100,000	83.09	16.91	
BMI (kg/m^2)	Underweight	75.95	24.05	<0.001
	Normal weight †	84.72	15.28	
	Overweight	78.64	21.36	
	Obese	67.56	32.44	
Physical activity	Yes†	84.36	15.64	<0.001
	No	74.58	25.42	
Education	>Secondary school †	78.72	21.28	0.660
	≤Secondary school	77.87	22.13	
Smoking status	No/former †	77.74	22.26	0.137
	Current smoker	76.27	23.73	
Alcohol status	No/former †	74.15	25.85	0.155
	Current drinker	77.6	22.4	

† Reference value; BMI, body mass index; CAD, Canadian dollars; $p \leq 0.05$.

A lower prevalence of CDs was observed among Chinese, Blacks, Filipinos, Arabs, and the "all other ethnicities" group compared with the white group (Table A2). The prevalence of CDs based on region and place of birth is presented in Table A3. Those born in South/Central America, the Caribbean, Africa, and Asia had a lower prevalence of CDs than those born in Canada and North America. A detailed analysis based on the country of birth showed that, compared with native-born Canadians, more participants born in Italy had CDs and fewer of those born in the Philippines had CDs.

Compared with non-immigrants, immigrants had a lower prevalence of heart disease, cancer, asthma, inflammatory lung diseases, and CDs but a higher prevalence of vitD insufficiency (52.82 vs. 31.75, $p < 0.001$). Immigrants also had lower mean concentration levels of S-25(OH)D, serum hs-CRP, and Hb and higher mean levels of HbA1c, the TC/HDL ratio, and ferritin than non-immigrants (Table 2).

Table 2. Weighted prevalence of chronic diseases, chronic-disease-related biomarkers, and self-rated general and mental health by immigration status.

		Non-Immigrants † (78.1%), %	Immigrants (21.9%), %	All Participants, (100%), %	*p*-Value
Diabetes	(Yes)	4.82	6.59	5.21	0.095
Heart disease	(Yes)	3.55	2.37	3.29	0.029
Cancer	(Yes)	6.41	4.65	6.02	0.041
Asthma	(Yes)	11.46	5.06	10.05	<0.001
Inflammatory lung diseases [a]	(Yes)	3.86	1.95	3.34	0.028
CDs [b]	(Yes)	23.2	16.64	21.72	<0.001
Self-rated general health	(Poor/fair)	9.67	11.67	10.11	0.121
Self-rated mental health	(Poor/fair)	8.31	6.76	7.95	0.334
S-25(OH)D, nmol/L	(<50)	31.75	52.82	36.34	<0.001
CD-Related Biomarkers		**Non-Immigrants † Mean (SE)**	**Immigrants Mean (SE)**	**95% CI**	***p*-Value**
Serum vitD	S-25(OH)D (nmol/L)	62.72 (1.73)	51.23 (1.41)	8.37, 14.62	<0.001
Glucose homeostasis	HbA1c (%)	5.39 (0.03)	5.52 (0.04)	−0.19, −0.07	<0.001
Lipid profile	TC/HDL ratio	3.63 (0.035)	3.79 (0.07)	−0.30, −0.02	0.030
Immune system and inflammation	hs-CRP (mg/L)	2.46 (0.07)	2.12 (0.13)	0.06, 0.6	0.017
	IgE (IU/mL)	118.37 (6.46)	102.75 (6.59)	−1.14, 32.38	0.066
Hematology	Ferritin (µg/L)	103.07 (2.42)	123.07 (6.20)	−34.45, −5.54	0.009
	Hb (g/L)	140.54 (0.43)	137.73 (0.70)	1.22, 4.42	0.001

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age > 29 years); [b] CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). † Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

Immigrants with diabetes, heart disease, and poor/fair self-reported general and mental health had lower S-25(OH)D levels than non-immigrants. More immigrants with diabetes, heart disease, cancer, asthma, inflammatory lung diseases, CDs, and poor/fair general or mental health had insufficient vitD levels compared with non-immigrants. However, there was no difference in vitD supplement use for any health indicators between immigrants and non-immigrants (Table 3).

There were no differences in S-25(OH)D levels between patients diagnosed before and after immigration for these health indicators (Table 4). There were no dates of diagnosis for inflammatory lung diseases, CDs, and self-reported general and mental health.

The results shown in Appendix A and Tables A4–A7 represent all study participants and are not stratified by immigration status or CDs. No differences were observed in mean S-25(OH)D levels by recent or long-term diagnosis (Table A4). The data were not analyzed for inflammatory lung diseases, CDs, and self-reported general and mental health because the date of diagnosis was not given.

The mean values for S-25(OH)D, vitD status (sufficiency/insufficiency), and the use of vitD supplements for each health indicator, including CDs, are presented in Table A5. Patients diagnosed with diabetes had insufficient vitD compared with those without diabetes. Patients with heart disease, CDs, and who self-reported poor/fair general health had higher S-25(OH)D levels than their counterparts without heart disease or CDs and with good general health. Patients with cancer tended to use more supplements than those without cancer. In addition, the mean concentration levels of S-25(OH)D, HbA1c, and IgE were higher among patients with CDs than among those without CDs (Table A6).

Table 3. Weighted mean 25(OH)D (nmol/L), prevalence of vitD insufficiency (<50 nmol/L), and vitD supplement use by immigration status.

	S-25(OH)D, (nmol/L)				<50 (nmol/L)			vitD Supplement Use		
	Non-Immigrant † Mean (SE)	**Immigrant Mean (SE)**	**95% CI**	***p*-Value**	**Non-Immigrant † %**	**Immigrant %**	***p*-Value**	**Non-Immigrant † %**	**Immigrant %**	***p*-Value**
Diabetes	65.30 (4.05)	47.56 (4.46)	−31.35, −4.13	0.013	31.43	61.63	<0.001	5.28	6.31	0.642
Heart disease	66.63 (2.15)	57.87 (3.80)	−17.42, −0.11	0.048	32.12	38.38	<0.001	[c]	[c]	
Cancer	70.71 (2.86)	67.96 (5.71)	−16.49, 10.98	0.681	29.08	32.28	<0.001	5.02	8.14	0.083
Asthma	59.13 (2.37)	54.23 (3.36)	−12.97, 3.18	0.222	30.68	53.59	<0.001	[c]	[c]	
Inflammatory lung diseases [a]	63.87 (1.80)	53.27 (5.80)	−22.09, 0.88	0.069	30.76	3841	<0.001	[c]	[c]	
CDs [b]	62.18 (1.80)	56.29 (2.49)	−11.23, −0.53	0.033	31.35	47.38	<0.001	4.91	4.97	0.379
Self-rated general health (poor/fair)	58.69 (1.94)	48.68 (2.98)	3.61, 16.43	0.004	31.13	61.2	<0.001	5.28	4.37	0.807
Self-rated mental health (poor/fair)	59.83 (2.43)	47.55 (3.75)	4.12, 20.45	0.005	32.52	64.39	<0.001	5.67	3.67	0.271

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age > 29 years). [b] CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). [c] Data are not sufficient for analysis. [†] Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

Table 4. Weighted mean 25(OH)D (nmol/L) based on the time of diagnosis (before or after immigration).

	S-25(OH)D, (nmol/L)			
	Before Immigration † Mean (SE)	**After Immigration Mean (SE)**	**95% CI**	***p*-Value**
Diabetes	41.80 (3.87)	48.48 (5.31)	−20.59, 7.24	0.331
Heart disease	44.38 (8.01)	59.55 (4.346)	−35.52, 5.18	0.136
Cancer	71.37 (16.93)	67.8 (5.95)	−36.74, 43.80	0.858
Asthma	52.82 (5.88)	56.57 (4.63)	−18.74, 11.25	0.609

† Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

The linear regression analysis showed that when the concentration levels of S-25(OH)D increased by 1 nmol/L, HbA1c, the TC/HDL ratio, IgE, ferritin, and Hb decreased (Table A7). In the multivariable logistic regression analysis, S-25(OH)D was associated with the prevalence of CDs (unadjusted OR: 1.006; 95%CI: 1.00, 1.01; $p = 0.007$) (result not shown). After adjusting for covariates (Table 5), the final model indicated there was no association between S-25(OH)D and CDs (OR: 1.007; 95%CI: 1.00, 1.01; $p = 0.070$). Immigrants were healthier (OR for CDs decreased by 60%) than non-immigrants. We also found that when age increased by 1 year, the OR for CDs increased by 2%. The OR increased by 71% among obese participants, by 174% when the HbA1c increased by 1%, and by 0.001% when IgE increased by 1 IU/mL.

Table 5. Multivariable logistic regression analysis for chronic diseases and serum 25(OH)D (contentious) in a predefined model.

		CDs		
		OR (SE)	**95% CI**	***p*-Value**
S-25(OH)D, nmol/L	1 nmol/L	1.007 (0.004)	1.00, 1.01	0.070
Immigration status	Immigrants	0.40 (0.09)	0.25, 0.63	<0.001
Age, years	1 year	1.02 (0.008)	1.00, 1.04	0.024
Sex	Female	0.86 (0.18)	0.56, 1.33	0.494
Household income, CAD (reference < 50,000)	50,000–100,000	0.61 (0.11)	0.42, 0.88	0.011
	≥100,000	0.56 (0.15)	0.32, 0.99	0.046
Ethnic group	Non-white	1.00 (0.29)	0.54, 1.86	0.998
BMI, kg/m^2 (reference normal weight)	Obese	1.92 (0.47)	1.15, 3.20	0.014
Met physical activity recommendations	No	0.80 (0.21)	0.46, 1.38	0.408
Education	≤Secondary school	0.97 (0.19)	0.69, 1.39	0.841
Smoking status	Current smoker	1.45 (0.34)	0.89, 2.36	0.126
Alcohol	Current drinker	0.64 (0.17)	0.37, 1.12	0.114
VitD supplement or analog use	Yes	0.83 (0.25)	0.45, 1.54	0.540
HbA1c (%)	1%	2.63 (0.37)	1.96, 3.51	<0.001
IgE (IU/mL)	1 IU/mL	1.01 (0.00)	1.00, 1.001	0.001
TC/HDL ratio	Ratio	0.98 (0.10)	0.80, 1.21	0.843
hs-CRP mg/L	1 mg/L	1.01 (0.04)	0.92, 1.10	0.889
Ferritin (μg/L)	1 μg/L	1.00 (0.00)	1.00, 1.001	0.380

Table 5. *Cont.*

		CDs		
		OR (SE)	**95% CI**	***p*-Value**
Hb (g/L)	1 g/L	0.98 (0.01)	0.97, 1.00	0.060
Constant		0.005 (0.01)	0.000, 0.10	0.001

CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). Adjusted for immigration status, age, sex, household income, education, ethnicity, BMI, physical activity, smoking behavior, alcohol consumption, vitD supplement use, HbA1c (glycated hemoglobin), TC/HDL-R (total cholesterol/high-density lipoprotein cholesterol ratio), Hb (hemoglobin), ferritin, IgE (immunoglobulin E), and hs-CRP (high-sensitivity C-reactive protein).

4. Discussion

This study used data for a large population of native-born Canadians and immigrants from 153 countries. Immigrants had a lower prevalence of CDs than native-born Canadians, including heart disease, cancer, asthma, and inflammatory lung diseases. Immigrants who came to Canada aged $\geq$ 18 years had more CDs than those younger than 18 years. There was no difference in the prevalence of CDs before immigration compared with post immigration. However, using two different time points (5 and 10 years), we found that the longer immigrants had lived in Canada, the higher the prevalence of CDs, which may be considered an early sign of health deterioration. Although the CHMS used a cross-sectional design, we used proxy indicators to verify the existence of the healthy immigrant effect (immigrants' health advantage in Canada).

Our results were consistent with those of Vang et al. (2015) who conducted a systematic review involving 77 studies of migration and health in Canada. That study found the healthy immigrant effect was more noticeable among recent immigrants and gradually disappeared among immigrants that were well-established in the host country. Moreover, the advantage of the healthy immigrant effect was also found in terms of protecting immigrants against CDs, including cancer, diabetes, heart disease, asthma, and obesity [6]. Those authors indicated there was a significant deviation for morbidity over time in the healthy immigrant effect, and there were no identifiable underlying reasons for health deterioration [6]. Moreover, Paszat et al. (2017) found that immigration was a determinant for developing colorectal cancer after the first 10 years of arrival in Canada [42]. Another study reported that Canadian immigrants demonstrated lower cancer-specific mortality, but this benefit diminished over time. After adjusting for age, each year following arrival was associated with increased mortality [43].

We hypothesized that lower S-25(OH)D levels, along with environmental and behavioral changes, may explain health deterioration. However, the relationship between vitD and CDs and the acculturation process may be affected by many factors, such as whether immigrants adopted healthy or unhealthy behaviors after immigration compared with before immigration. For example, in previous immigration, acculturation, and vitD studies, it was reported that immigrants less frequently consumed vitD-rich foods, engaged in less physical activity, and were less exposed to sun than non-immigrants [2,6]. Other studies found the length of residency since immigration was a crucial indicator of lifestyle acculturation. Higher acculturation levels were associated with significantly higher S-25(OH)D [2,5,44].

This study found that, compared with non-immigrants, immigrants had lower mean S-25(OH)D levels and more vitD insufficiency. Similarly, immigrant patients with CDs (e.g., diabetes, heart diseases, cancer, asthma, and inflammatory lung diseases) and poor/fair self-reported general and mental health had higher insufficiency levels than non-immigrants. In a systematic review and meta-analysis of 95 studies (880,128 participants), Chowdhury et al. (2014) reported an inverse association between circulating S-25(OH)D and the risk for death due to cardiovascular disease, cancer, and other mortality causes. Moreover, vitD3 supplementation was inversely associated with lower overall mortality among older adults [17]. Several other studies, including reviews, found that inadequate S-25(OH)D concentration

was associated with an increased risk of CDs [26,27]. Despite the high level of evidence supporting these findings, there remains some controversy regarding the causative nature and efficacy of vitD. For example, there was a two-way correlation between vitD deficiency and disease outcomes such as infectious diseases, rheumatoid arthritis, and obesity [45].

Our previous findings indicated that immigrants had higher S-25(OH)D levels the longer they lived in Canada [2]. To gain better insights about the relationship between the duration of diagnoses and the prevalence of CDs and S-25(OH)D levels, we hypothesized that those who were recently ($\leq$1 year or $\leq$5 years) diagnosed would have lower S-25(OH)D levels than those with a long duration of diagnosis (>1 year or >5 years). A previous study reported that S-25(OH)D may be sensitive to changes in health status [19]. However, our analysis revealed no difference in S-25(OH)D between recently diagnosed patients and their counterparts with a longer time since diagnosis.

Another study recommended investigating pre-and post-migration experiences to better understand the healthy immigrant effect and health changes over time in the host country [6]. Therefore, we evaluated the prevalence of CDs and pre-and post-immigration vitD by the date of diagnosis and date of immigration. The results showed no differences in mean S-25(OH)D among immigrants diagnosed before immigration compared with those diagnosed after immigration for any of the studied health indicators (diabetes, heart disease, cancer, and asthma).

We assumed that having lower S-25(OH)D levels (deficient or insufficient vitD) for a long time may increase the risk of a CD diagnosis. Therefore, we investigated the relationships between the length of time since immigration and vitD status and CDs. Our results showed that the longer the time after immigration, the higher the prevalence of CDs among immigrants.

Our univariate analyses showed that the mean concentrations of CD-related biomarkers (HbA1c, hs-CRP, and IgE) were higher among patients with CDs compared with those without CDs. We did not expect to find the mean concentration of S-25(OH)D was higher among patients with CDs compared with their non-CD counterparts: mean (SE) 63.118 (1.787) versus 59.42 (1.76) (95%CI: -6.27, -1.13; $p = 0.007$). However, the findings related to immigration status and the use of vitD supplements along with other covariates may change the direction of the relationship between CDs and S-25(OH)D. For example, non-immigrants had more CDs and higher S-25(OH)D, and patients with CDs used more vitD supplementation than those without CDs. After adjusting for immigration status, vitD supplementation, and other covariates, S-25(OH)D was not associated with CDs, although HbA1c and IgE remained associated with a higher prevalence of CDs.

Our analysis showed a negative association between S-25(OH)D and HbA1c, the TC/HDL ratio, IgE, ferritin, and Hb levels. Using the same data for Canadian adults, another study found the same inverse association between S-25(OH)D and elevated ferritin [46]. In addition, vitD supplementation was found to improve S-25(OH)D levels among patients with diabetes with vitD deficiency [47]. Our investigation of the concentrations of these biomarkers among immigrants compared with non-immigrants showed that immigrants had higher concentrations of HbA1c, and ferritin, a higher TC/HDL ratio, and lower levels of hs-CRP and Hb than non-immigrants. These deviations in CD-related biomarkers may be a preliminary indicator for the decline in the health status of immigrants in the long term.

Our univariate analyses revealed that immigrants with insufficient vitD were more likely to self-report poor/fair general and mental health than non-immigrants. Previous studies hypothesized that low vitD concentration was associated with depression [48,49]. Another study found that anxiety, depression, and health-related quality of life were not associated with S-25(OH)D levels among the immigrant population [50]. Our analysis revealed that the prevalence of CDs was higher among those with older age, lower household income, and obesity. White ethnic groups had a higher prevalence of CDs than non-white groups, and CDs varied among immigrants from different ethnic groups and countries and regions of birth. Our finding concerning the health advantage of being immigrants

(i.e., fewer CDs) was observed among Chinese, Black, Filipino, and Arab ethnicities as well as those born in South/Central America and the Caribbean, Africa, Asia, and the Philippines. In contrast, this effect was less consistent (i.e., more CDs) for those born in Italy. However, the difference in health status among immigrants may reflect variations in acculturation. The effect of origin in terms of health, life expectancy, and mortality patterns among immigrant populations varies across different ethnic groups [51].

There was no association between S-25(OH)D and CDs in our adjusted regression model. However, in addition to the environmental and lifestyle changes after immigration, we assumed the cumulative impact of immigrants' lower levels of S-25(OH)D and the deviation in CD-related biomarkers over time played a crucial role in the subsequent health deterioration among immigrants in terms of the investigated proxy indicators. Furthermore, we assumed that improving S-25(OH)D over time, as found in our previous analysis [2], did not enhance the deviated biomarkers or cure CDs once they had developed. In a randomized control trial, vitD supplementation for patients with type 2 diabetes and asymptomatic vitD deficiency did not improve HbA1c levels [47].

However, considering the consistency of results related to higher deficiency levels of S-25(OH)D among immigrants and the relatively new findings relating to vitD and health deterioration, we cannot quantify the degree and time of deterioration nor guarantee such an association. Therefore, we recommend further research on this topic using longitudinal designs. Immigrants can be followed over their residency time in the host country to explain the patterns, developments, and direction of health deterioration.

Cross-sectional surveys such as the CHMS are not usually used to examine changes in health over time. The bidirectional association between serum S-25(OH)D and CDs is complex, and it is challenging to address residual confounding using an observational study design. Longitudinal observation and interventional trials are warranted to further understand the relationship between S-25(OH)D and immigrants' health deterioration.

A limitation of using secondary data is that some of the chronic diseases could not be included in the analysis because the date of diagnosis was not provided. The CHMS data did not differentiate immigrants by specific immigration class or type (e.g., refugees, family class, economic migrants, or asylum seekers). Moreover, native-born Canadians formed a single group, despite some being second- or third-generation immigrants; this resulted in a high level of heterogeneity in the reference population. Previous immigration studies recommended assessing vitD status and its determinants among subgroups living in the same country [52]. To compare the same generation of immigrants rather than aggregated generations [53], it will be necessary to gather evidence and formulate recommendations specific to sub-populations that may differ from the overall immigrant population [32].

5. Conclusions

This study confirmed that the current health status of immigrants is good (healthy), but over time they may experience more CDs than their non-immigrant counterparts. S-25(OH)D is associated with environmental and behavioral factors and acts as a biological measure but is not associated with immigrants' current health status. However, in addition to the adoption of unhealthy diets and lifestyles, lower levels of accumulated S-25(OH)D may impact the health profile of immigrants in terms of CD-related biomarkers. This may partially explain immigrants' health deterioration over time. Given the emerging research interest in immigrants' health deterioration, we recommend further longitudinal research to investigate the relationship between vitD and health deterioration, accounting for the dietary and lifestyle acculturation process.

Summary of Key Issues and Findings

Extensive research evidence indicates that Canadian immigrants tend to be healthier at the time of immigration than well-established immigrants and non-immigrants. This "healthy immigrant" effect lessens over time for immigrants living in Canada. Nevertheless, immigrants are at higher risk for vitD deficiency compared with non-immigrants, with

the risk highest in younger and more recent immigrants. The longer an immigrant lived in Canada, the better their serum vitD levels; ethnicity was also a significant indicator of vitD deficiency.

This study highlighted that immigrants tend to have better health than their counterparts in terms of the prevalence of chronic diseases (CDs) such as heart disease, cancer, asthma, and inflammatory lung diseases, but there is no difference in self-rated general and mental health. In contrast, CD-related biomarkers (e.g., glycated hemoglobin and total cholesterol/high-density lipoprotein cholesterol ratio) and serum vitD differed in favor of non-immigrants. There was no difference in the pre-migration prevalence of CDs compared with post-immigration; however, the longer immigrants lived in Canada, the higher the prevalence of CDs. The adjusted regression model showed serum vitD was not associated with CDs. Our findings suggest the cumulative impact of lower serum vitD among immigrants over time, changing biomarkers, and environmental and lifestyle changes after immigration may play crucial roles in subsequent health deterioration among immigrants.

Further longitudinal research is needed to clarify immigrants' health deterioration and the complicated and controversial bidirectional association between serum vitD and CDs. For instance, immigrants may be followed over their residency in their host country to explore the patterns, developments, and direction of health deterioration.

Author Contributions: S.Y. and G.A.W. conceived this study with close supervision from G.A.W.; S.Y. managed the data, verified the analytical methods, and prepared the tables and figures; A.H. verified the underlying data at the research data center; S.Y. interpreted the results and prepared the final draft; All authors, including I.C., M.P., D.M. and M.F., contributed to the design and analysis of the research and the substantive review of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement: All components of the national survey were reviewed and authorized annually by the Health Canada/Public Health Agency of Canada Research Ethics Board (REB# 2005-0025). The Health Canada Research Ethics Board approved the CHMS.

Informed Consent Statement: Statistics Canada collected written consent from all participants for a personal interview, physical measures, and biospecimen collection.

Data Availability Statement: The data described in the manuscript, codebook, and analytic codes are not publicly available because the data are confidential national data hosted by Statistics Canada.

Acknowledgments: The authors acknowledge the Carleton, Ottawa, Outaouais Local Research Data Centre team for assistance with access to the CHMS data. The CHMS data were obtained and supported by funding to the Canadian Research Data Network from the Social Sciences and Humanities Research Council, the Canadian Institute for Health Research, the Canadian Foundation for Innovation, and Statistics Canada. Although the research and analysis were based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Supporting Information Including (Tables A1–A7).

Table A1. Biomarker details.

Biomarkers	Symbol	Unit	Method of Measurements/Name of the Machine and Related Information	Analytical Detection Limit	CHMS Reference Laboratory Precision Target
Serum 25-hydroxyvitamin D [2,54]	S-25(OH)D	nmol/L	Chemiluminescent immunoassay technology (DiaSorin, Ltd., Stillwater, MN, USA)	10–375	<20 nmol/L = 15% 20–100 nmol/L = 10% >100 nmol/L = 12%
Glycated hemoglobin	HbA1c	%	Immunoturbidimetric end-point spectrophotometry (anti-HbA1c antibody, polyhapten) on the Ortho Clinical Diagnostics Vitros 5, 1FS analyzer. %A1c is a derived test calculated from the quantitative measurements of hemoglobin and hemoglobin A1c	Hb: 6.0–22.0 g/dL(component) HbA1c: 0.2–2.5 g/dL (component) %A1c: 4–14% NGSP	5%
Total cholesterol/HDL cholesterol ratio	TC/HDL ratio		Derived calculation	N/A	N/A
High-sensitivity C-reactive protein	hs-CRP	mg/L	Immunoturbidimetric two-point rate reflectance spectrophotometry (monoclonal antibodies) on the Ortho Clinical Diagnostics Vitros 5, 1FS analyzer	0.10–15.0	5%
Total immunoglobulin E	IgE	IU/mL	Two-site sandwich immunoassay using direct chemiluminescent technology on the Siemens ADVIA Centaur XP analyzer	1.5–3300	10%
Ferritin	Ferritin	µg/L	Two-site sandwich immunoassay using direct chemiluminescent technology on the Siemens ADVIA Centaur XP analyzer	0.5–1650	10%
Hemoglobin	Hb	g/L	Hemoglobin is a non-cyanide-based method read photometrically at 555 nm on the POCH-i100 Sysmex hematology analyzer	0–25.0	1.5%

Table A2. Weighted prevalence of chronic diseases by ethnicity.

	No CDs (78.3%), %	**CDs (21.7%), %**	***p*-Value**
White †	76.72	23.28	-
Aboriginal	74.47	25.53	0.446
South Asian	80.85	19.15	0.309
Chinese	86.08	13.92	0.014
Black	89.33	10.67	0.002
Filipino	89.77	10.23	0.011
Latin American	86.48	13.52	0.155
Arab	88.92	11.08	0.049
Southeast Asian	83.78	16.22	0.137
West Asian	90.89	9.11	0.196
Japanese	60.2	39.8	0.141
Multiple ethnicities	72.13	27.87	0.250
Other ethnicities	84.05	15.95	<0.001

CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). † Reference value; $p \leq 0.05$. Data for Koreans were insufficient for analysis.

Table A3. Weighted prevalence of chronic diseases by country and region of birth.

		No CDs (78.3%), %	**CDs (21.7%), %**	***p*-Value**
Region of birth	Canada and North America †	76.53	23.47	-
	South/Central America and the Caribbean	86.75	13.25	0.011
	Europe	78.96	21.04	0.314
	Africa	88.74	11.26	0.008
	Asia	85.94	14.06	0.006
Country of birth	Canada †	76.39	23.61	-
	China	80.81	19.19	0.575
	USA	84.31	15.69	0.224
	France	89.7	10.3	0.066
	Jamaica	81.21	18.79	0.648
	UK	72.97	27.03	0.397
	Mexico	81.54	18.46	0.527
	Netherlands	60.97	39.03	0.155
	India	82.51	17.49	0.115
	Philippines	94.64	5.36	<0.001
	Hong Kong	77.8	22.2	0.907
	Germany	72.55	27.45	0.625

Table A3. *Cont.*

	No CDs (78.3%), %	CDs (21.7%), %	*p*-Value
Italy	53.56	46.44	0.004
Iran	84.93	15.07	0.537
Lebanon	49.67	50.33	0.126
Others	87.37	12.63	<0.001

CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). † Reference value; $p \leq 0.05$. The data for Algeria, Pakistan, Romania, Colombia, and Morocco were insufficient for analysis.

Table A4. Weighted mean 25(OH)D for each chronic disease based on the date of diagnosis: recent (e.g., ≤1 year) versus long-term (e.g., >1 year).

	S-25(OH)D, (nmol/L)											
	Diagnosis ≤ 1 year †		Diagnosis > 1 year				Diagnosis ≤ 5 years †		Diagnosis > 5 years			
	%	Mean (SE)	%	Mean (SE)	95% CI	*p*-Value	%	Mean (SE)	%	Mean (SE)	(95% CI)	*p*-Value
Diabetes	9.47	45.63 (10.28)	90.53	62.58 (3.16)	−38.21, 4.31	0.113	61.8	64.80 6.41)	38.92	58.52 (3.15)	−8.07, 20.62	0.374
Heart disease	7.17	58.00 (5.97)	92.83	65.80 (1.98)	−20.58, 4.99	0.220	69.32	63.19 (2.58)	30.68	66.14 (2.04)	−7.78, 1.88	0.218
Cancer	11.78	75.47 (3.82)	88.22	69.55 (2.68)	−2.93, 14.76	0.179	59.76	66.89 (3.82)	40.24	72.44 (3.34)	−16.57, 5.47	0.308
Asthma	3.56	61.17 (4.50)	96.44	57.82 (2.34)	−5.19, 11.89	0.425	83.21	61.12 (2.78)	16.79	57.31 (2.43)	−1.19, 8.81	0.129

† Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval.

Table A5. Weighted mean and status of 25(OH)D for each chronic disease and the use of vitD supplements.

		25(OH)D, (nmol/L)			S-25(OH)D Status			VitD Supplements		
		Mean (SE)	95% CI	*p*-Value	≥50 nmol/L, %	<50 nmol/L, %	*p*-Value	No, %	Yes, %	*p*-Value
Diabetes	No †	60.23 (1.66)			64.14	35.86		94.84	5.16	
	Yes	60.32 (3.15)	−5.08, 4.89	0.968	55.11	44.89	0.043	92.6	7.54	0.142
Heart disease	No †	60.04 (1.72)			63.24	36.76		94.92	5.08	
	Yes	65.21 (1.94)	−9.42, −0.91	0.020	75.78	24.22	0.005	88.56	11.44	0.102
Cancer	No †	59.51 (1.78)			62.84	37.16		95.04	4.96	
	Yes	70.23 (2.46)	−16.44, −4.99	0.001	74.76	25.24	0.068	89.06	10.94	0.025
Asthma	No †	60.40 (1.69)			64.22	35.78		94.51	5.49	
	Yes	58.57 (2.20)	−1.02, 4.68	0.197	58.68	41.32	0.095	96.80	3.20	0.104
Inflammatory lung diseases [a]	No †	60.90 (1.70)			64.11	35.89		92.80	7.20	
	Yes	61.74 (2.38)	−5.03, 3.36	0.685	61.92	38.08	0.538	84.99	15.01	0.161
CDs [b]	No CDs †	59.41(1.76)			63.41	36.59		95.11	4.89	
	CDs	63.11(1.79)	−6.27, −1.13	0.007	64.59	35.41	0.5945	93.19	6.81	0.119
Self-rated general health	Good †	56.35 (2.01)			64.4	35.6		94.81	51.9	
	Poor/Fair	60.66 (1.73)	1.10, 7.52	0.011	56.98	43.02	0.023	94.00	6.00	0.479
Self-rated mental health	Good †	57.33 (2.24)			62.89	37.11		94.45	5.55	
	Poor/Fair	59.10 (1.70)	−1.11, 6.44	0.157	56.51	43.49	0.197	91.61	8.39	0.401

[a] Inflammatory lung diseases: bronchitis + chronic obstructive pulmonary disease + emphysema; (age > 29 years). [b] CDs (chronic diseases): at least one of the listed CDs (diabetes, heart disease, cancer, asthma, and inflammatory lung diseases). † Reference value; $p \leq 0.05$; SE, standard error; CI, confidence interval. Good = Excellent/Very Good/Good; <50 = Insufficient; ≥50 = Sufficient.

Table A6. Weighted means for biomarkers by the presence of chronic diseases.

		Chronic Diseases (CDs)			
		No CDs † Mean (SE)	**CDs Mean (SE)**	**95%CI**	**p-Value**
Serum vitD	S-25(OH)D, nmol/L	59.42 (1.76)	63.118 (1.787)	−6.27, −1.13	0.007
Glucose homeostasis	HbA1c, %	5.30 (0.2)	5.82 (0.05)	−0.62, −0.41	<0.001
Lipid profile	TC/HDL ratio	3.65 (0.03)	3.72 (0.07)	−0.20, 0.07	0.309
Immune system and inflammation	hs-CRP, mg/L	2.22 (0.08)	2.91 (0.14)	−1.03, −0.35	<0.001
	IgE, IU/mL	95.48 (5.85)	181.74 (20.96)	−134.29, −38.23	0.001
Hematology	Ferritin, µg/L	106.02 (2.57)	114.90 (5.02)	−20.95, 3.19	0.141
	Hb, g/L	139.84 (042)	140.22 (0.74)	−1.86, 1.12	0.609

† Reference value; $p \leq 0.05$; CDs, chronic diseases; SE, standard error; CI, confidence interval.

Table A7. Linear regression of S-25(OH)D and chronic-disease-related biomarkers.

		S-25(OH)D and CD-Related Biomarkers			
		Mean (SE)	**β (SE)**	**95%CI**	***p*-Value**
Serum vitD	S-25(OH)D, nmol/L	60.22 (1.69)	-	-	-
Glucose homeostasis	HbA1c, %	5.42 (0.03)	−1.79 (0.79)	−3.43, −0.142	0.035
Lipid profile	TC/HDL ratio	3.67 (0.03)	−4.09 (0.39)	−4.90, −3.28	<0.001
Immune system and inflammation	hs-CRP, mg/L	2.38 (0.07)	−0.50 (0.23)	−0.94, 0.02	0.058
	IgE, IU/mL	114.6 (5.55)	−0.01 (0.00)	−0.01, −0.00	0.007
Hematology	Ferritin, µg/L	108.05 (2.18)	−0.02 (0.00)	−0.03, −0.01	0.003
	Hb, g/L	139.93 (0.41)	−0.10 (0.04)	−0.19, −0.02	0.016

$p \leq 0.05$; SE, standard error; CI, confidence interval; CD, chronic disease.

References

1. Gushulak, B.D.; Williams, L.S. National Immigration Health Policy Existing Policy, Changing Needs, and Future Directions. *Can. J. Public Health* **2004**, *95*, I27–I29. [CrossRef] [PubMed]
2. Yousef, S.; Manuel, D.; Colman, I.; Papadimitropoulos, M.; Hossain, A.; Faris, M.; Wells, G. Vitamin D Status among First-Generation Immigrants from Different Ethnic Groups and Origins: An Observational Study Using the Canadian Health Measures Survey. *Nutrients* **2021**, *13*, 2702. [CrossRef] [PubMed]
3. StatisticsCanada. Population Projections for Canada, Provinces and Territories. 2014. Available online: https://www150.statcan.gc.ca/n1/en/pub/91-520-x/91-520-x2010001-eng.pdf?st=LWFifucU (accessed on 20 November 2021).
4. Newbold, B. The short-term health of Canada's new immigrant arrivals: Evidence from LSIC. *Ethn. Health* **2009**, *14*, 315–336. [CrossRef] [PubMed]
5. Sanou, D.; O'Reilly, E.; Ngnie-Teta, I.; Batal, M.; Mondain, N.; Andrew, C.; Newbold, B.K.; Bourgeault, I. Acculturation and Nutritional Health of Immigrants in Canada: A Scoping Review. *J. Immigr. Minority Health* **2014**, *16*, 24–34. [CrossRef] [PubMed]
6. Vang, Z.; Sigouin, J.; Flenon, A.; Gagnon, A. The Healthy Immigrant Effect in Canada: A Systematic Review. *Popul. Change Lifecourse Strateg. Knowl. Clust. Discuss. Pap. Ser. Réseau Strat. Connaiss. Changements Popul. Parcour. Vie Doc. Trav.* **2015**, *3*, 4.
7. Autier, P. Vitamin D status as a synthetic biomarker of health status. *Endocrine* **2016**, *51*, 201–202. [CrossRef]
8. Chiu, M.; Austin, P.C.; Manuel, D.; Tu, J.V. Cardiovascular Risk Factor Profiles of Recent Immigrants vs Long-term Residents of Ontario: A Multi-Ethnic Study. *Can. J. Cardiol.* **2012**, *28*, 20–26. [CrossRef]
9. Kinnon, D. *Canadian Research on Immigration and Health*; Cat. No H21-149/1999E; Health Canada: Ottawa, ON, Canada, 1999.
10. Williams, D.R.; Mohammed, S.A.; Leavell, J.; Collins, C. Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities. *Ann. N. Y. Acad. Sci.* **2010**, *1186*, 69–101. [CrossRef]
11. Martin, C.A.; Gowda, U.; Renzaho, A.M.N. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. *Nutrition* **2016**, *32*, 21–32. [CrossRef]
12. Spiro, A.; Buttriss, J.L. Vitamin D: An overview of vitamin D status and intake in Europe. *Nutr. Bull.* **2014**, *39*, 322–350. [CrossRef]
13. Centers for Disease, Control Prevention. *Guidelines for Evaluation of the Nutritional Status and Growth in Refugee Children during the Domestic Medical Screening Examination*; Centers for Disease, Control Prevention, Division of Global Migration and Quarantine: Atlanta, GA, USA, 2013.

14. Granlund, L.; Ramnemark, A.; Andersson, C.; Lindkvist, M.; Fhärm, E.; Norberg, M. Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden. *Eur. J. Clin. Nutr.* **2016**, *70*, 373–379. [CrossRef] [PubMed]
15. De Boer, I.H.; Kestenbaum, B.; Shoben, A.B.; Michos, E.D.; Sarnak, M.J.; Siscovick, D.S. 25-Hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. *J. Am. Soc. Nephrol.* **2009**, *20*, 1805–1812. [CrossRef] [PubMed]
16. Zmijewski, M.A. Vitamin D and Human Health. *Int. J. Mol. Sci.* **2019**, *20*, 145. [CrossRef] [PubMed]
17. Chowdhury, R.; Kunutsor, S.; Vitezova, A.; Oliver-Williams, C.; Chowdhury, S.; Kiefte-de-Jong, J.C.; Khan, H.; Baena, C.; Prabhakaran, D.; Hoshen, B.; et al. Vitamin D and risk of cause specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* **2014**, *348*, g1903. [CrossRef] [PubMed]
18. Holick, M.F. The Vitamin D Defi ciency Pandemic: A Forgotten Hormone Important for Introduction: Historical Perspective. *Public Health Rev.* **2010**, *32*, 267–283. [CrossRef]
19. McNeill, G.; Vyvyan, J.; Peace, H.; McKie, L.; Seymour, G.; Hendry, J.; MacPherson, I. Predictors of micronutrient status in men and women over 75 years old living in the community. *Br. J. Nutr.* **2002**, *88*, 555–561. [CrossRef]
20. Sun, Y.-Q.; Langhammer, A.; Skorpen, F.; Chen, Y.; Mai, X.-M. Serum 25-hydroxyvitamin D level, chronic diseases and all-cause mortality in a population-based prospective cohort: The HUNT Study, Norway. *BMJ Open* **2017**, *7*, e017256. [CrossRef]
21. Gaksch, M.; Jorde, R.; Grimnes, G.; Joakimsen, R.; Schirmer, H.; Wilsgaard, T.; Mathiesen, E.B.; Njølstad, I.; Løchen, M.-L.; März, W.; et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26,916 individuals from a European consortium. *PLoS ONE* **2017**, *12*, e0170791. [CrossRef]
22. Jablonski, N.G.; Chaplin, G. Human skin pigmentation, migration and disease susceptibility. *Philos. Trans. R. Soc. B Biol. Sci.* **2012**, *367*, 785–792. [CrossRef]
23. Heaney, R.P.; Holick, M.F. Why the IOM recommendations for vitamin D are deficient. *J. Bone Miner. Res.* **2011**, *26*, 455–457. [CrossRef]
24. Pham, T. Vitamin D Status of Immigrant and Ethnic Minority Children Ages 2 to 5 y in Montréal. Ph.D. Thesis, McGill University, Montreal, QC, Canada, 2012.
25. Mithal, A.; Wahl, D.A.; Bonjour, J.P.; Burckhardt, P.; Dawson-Hughes, B.; Eisman, J.A.; El-Hajj Fuleihan, G.; Josse, R.G.; Lips, P.; Morales-Torres, J. Global vitamin D status and determinants of hypovitaminosis D. In *Osteoporosis International*; Springer: London, UK, 2009; pp. 1807–1820.
26. Peterlik, M.; Boonen, S.; Cross, H.S.; Lamberg-Allardt, C. Vitamin D and calcium insufficiency-related chronic diseases: An emerging world-wide public health problem. *Int. J. Environ. Res. Public Health* **2009**, *6*, 2585–2607. [CrossRef] [PubMed]
27. Renzaho, A.M.N.; Bhsci, J.A.H.; Nowson, C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: A systematic review. *Nutrition* **2011**, *27*, 868–879. [CrossRef] [PubMed]
28. Cristian Ilie, P.; Stefanescu, S.; Smith, L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin. Exp. Res.* **2020**, *32*, 1195–1198. [CrossRef] [PubMed]
29. Ghasemian, R.; Shamshirian, A.; Heydari, K.; Malekan, M.; Alizadeh-Navaei, R.; Ebrahimzadeh, M.A.; Warkiani, M.E.; Jafarpour, H.; Bazaz, S.R.; Shahmirzadi, A.R.; et al. The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis. *MedRxiv* **2021**. [CrossRef]
30. Mercola, J.; Grant, W.B.; Wagner, C.L. Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. *Nutrients* **2020**, *12*, 3361. [CrossRef]
31. Meltzer, D.O.; Best, T.J.; Zhang, H.; Vokes, T.; Arora, V.; Solway, J. Association of Vitamin D Status and Other Clinical Characteristics with COVID-19 Test Results. *JAMA Netw. Open* **2020**, *3*, e2019722. [CrossRef] [PubMed]
32. Yousef, S.; Elliott, J.; Manuel, D.; Colman, I.; Papadimitropoulos, M.; Hossain, A.; LeClair, N.; Wells, G.A. Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations—A systematic review and meta-analysis. *Syst. Rev.* **2019**, *8*, 211. [CrossRef]
33. Levinsky, M.; Schiff, M. Lifetime cumulative adversity and physical health deterioration in old age: Evidence from a fourteen-year longitudinal study. *Soc. Sci. Med.* **2021**, *289*, 114407. [CrossRef]
34. Thacker, S.B.; Stroup, D.F.; Carande-Kulis, V.; Marks, J.S.; Roy, K.; Gerberding, J.L. Measuring the public's health. *Public Health Rep.* **2006**, *121*, 14–22. [CrossRef]
35. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *Bull. World Health Organ.* **2007**, *85*, 867–872. [CrossRef]
36. Day, B.; Langlois, R.; Tremblay, M.; Knoppers, B.M. Canadian Health Measures Survey: Ethical, legal and social issues. *Health Rep./Stat. Can. Can. Cent. Health Inf.* **2007**, *18*, 37–51.
37. Ng, E. *Canadian Health Measures Survey: A Tool for Immigrant Health Research*; Health Report; Statistics Canada: Ottawa, ON, Canada, 2015.
38. Dawson-Hughes, B. *Vitamin D deficiency in Adults: Definition, Clinical Manifestations, and Treatment-UpToDate*. Update-2021. 2021. Available online: https://www.uptodate.com/contents/vitamin-d-deficiency-in-adults-definition-clinical-manifestations-and-treatment?search=vitamin (accessed on 31 January 2022).
39. Ross, A.C.; Taylor, C.L.; Yaktine, A.L.; Del Valle, H.B. *Dietary Reference Intakes. Calcium Vitamin D Committee to Review Dietary Reference Intakes for Vitamin D and Calcium Food and Nutrition Board*; National Academies Press: Washington, DC, USA, 2011.

40. StatisticsCanada. *Canadian Health Measures Survey, Cycle 3—Privacy Impact Assessment. 2012–2013*; Statistics Canada: Ottawa, ON, Canada, 2013.
41. StatisticsCanada. *Canadian Health Measures Survey, Cycle 4, 2014–2015—Privacy Impact Assessment Summary*; Statistics Canada: Ottawa, ON, Canada, 2015.
42. Paszat, L.; Sutradhar, R.; Liu, Y.; Baxter, N.N.; Tinmouth, J.; Rabeneck, L. Risk of colorectal cancer among immigrants to Ontario, Canada. *BMC Gastroenterol.* **2017**, *17*, 85. [CrossRef] [PubMed]
43. Cheung, M.C.; Earle, C.C.; Fischer, H.D.; Camacho, X.; Liu, N.; Saskin, R.; Shah, B.R.; Austin, P.C.; Singh, S. Impact of immigration status on cancer outcomes in Ontario, Canada. *J. Oncol. Pract.* **2017**, *13*, e602–e612. [CrossRef] [PubMed]
44. Salant, T.; Diane, S.L. Measuring culture: A critical review of acculturation and health in Asian immigrant populations. *Soc. Sci. Med.* **2003**, *71*, 71–90. [CrossRef]
45. Spedding, S. *Vitamin D and Human Health*, 2015 ed.; MDPI: Basel, Switzerland; Beijing, China; Wuhan, China, 2015.
46. Munasinghe, L.L.; Ekwaru, J.P.; Mastroeni, M.F.; Mastroeni, S.S.B.S.; Veugelers, P.J. The association of serum 25-hydroxyvitamin D concentrations with elevated serum ferritin levels in normal weight, overweight and obese Canadians. *PLoS ONE* **2019**, *14*, e0213260. [CrossRef]
47. Randhawa, F.A.; Mustafa, S.; Khan, D.M.; Hamid, S. Effect of Vitamin D supplementation on reduction in levels of HbA1 in patients recently diagnosed with type 2 Diabetes Mellitus having asymptomatic Vitamin D deficiency. *Pak. J. Med. Sci.* **2017**, *33*, 881. [CrossRef]
48. Anglin, R.E.; Samaan, Z.; Walter, S.D.; McDonald, S.D. Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. *Br. J. Psychiatry* **2013**, *202*, 100–107. [CrossRef]
49. Chu, F.; Ohinmaa, A.; Klarenbach, S.; Wong, Z.-W.; Veugelers, P. Serum 25-Hydroxyvitamin D Concentrations and Indicators of Mental Health: An Analysis of the Canadian Health Measures Survey. *Nutrients* **2017**, *9*, 1116. [CrossRef]
50. Granlund, L.E.; Ramnemark, A.K.; Andersson, C.; Lindkvist, M.C.; Norberg, M.; Fhärm, E.M. Vitamin D status was not associated with anxiety, depression, or health-related quality of life in Middle Eastern and African-born immigrants in Sweden. *Nutr. Res.* **2020**, *75*, 109–118. [CrossRef]
51. Huh, J.; Prause, J.A.; Dooley, C.D. The impact of nativity on chronic diseases, self-rated health and comorbidity status of Asian and Hispanic immigrants. *J. Immigr. Minority Health* **2008**, *10*, 103–118. [CrossRef]
52. Hilger, J.; Friedel, A.; Herr, R.; Rausch, T.; Roos, F.; Wahl, D.A.; Pierroz, D.D.; Weber, P.; Hoffmann, K. A systematic review of vitamin D status in populations worldwide. *Br. J. Nutr.* **2014**, *111*, 23–45. [CrossRef] [PubMed]
53. Zhu, L. Depression risks and correlates among different generations of Chinese Americans: The effects of relationships with friends and relatives. *Soc. Sci.* **2017**, *6*, 56. [CrossRef]
54. Munasinghe, L.L.; Yuan, Y.; Willows, N.D.; Faught, E.L.; Ekwaru, J.P.; Veugelers, P.J. Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010. *Br. J. Nutr.* **2017**, *117*, 457–465. [CrossRef] [PubMed]

Systematic review

*Fields that have an **asterisk (*)** next to them means that they **must be answered. Word limits** are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section. Registrant means the person filling out the form*.

1. * Review title.

Give the title of the review in English

A Systematic Assessment of the Quality and Content of the Immigrant's Health and Vitamin D's Clinical Practice Guidelines (CPGs) using the AGREE II Instrument

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

English

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

15/12/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

14/06/2022

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.
Screening is going on

Screening is going on

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Said Yousef Abdelrazeq

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr. Abdelrazeq

7. * Named contact email.

Give the electronic email address of the named contact.

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

14 Nobleton Avenue, K1G 6A6, Ottawa, ON Canada

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

6138901454

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Ottawa-Heart Institute

Organisation web address:

None

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Said Yousef Abdelrazeq. University of Ottawa-Heart Institute
Ms Lamia Hayawi.
George A. Wells. University of Ottawa-Heart Institute

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Not available

Grant number(s)

State the funder, grant or award number and the date of award

Not applicable

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Do the Immigrants' and Vitamin Ds' clinical practice guidelines (CPGs) comply with AGREE II instrument quality standards?

Does the content of immigrants' clinical practice guidelines include recommendations on Vitamin D?

Does the content of vitamin Ds' clinical practice guidelines include recommendations for immigrants?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

The search strategy was developed in consultation with an experienced medical information specialist. Using the Ovid platform, we searched Ovid MEDLINE® ALL and Embase. Searches utilized a combination of controlled vocabulary (e.g., "Vitamin D", "Emigrants and Immigrants", "Refugees") and keywords (e.g., "vitamin d", "asylum seeker", "foreigner") and incorporated a CADTH-derived guideline filter. We also

searched for the Turning Research Into Practice (TRIP) database. All searches were completed on October 15, 2020. Results were limited to the publication from the years 2010 to the date of search.

Supplemented searching will be performed searching for key articles using the reference citation.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/240562_STRATEGY_20210305.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Migration is a risk factor for vitamin D deficiency. Immigrants worldwide have lower vitamin D levels due to changes in lifestyle, dietary intake, and other environmental factors. The systematic review will focus on the critical appraisal of vitamin D guidelines and the guidelines of immigrant's health using AGREE II instrument. Moreover, to evaluate the content whether the recommendations of vitamin D's guidelines covered immigrants and vice versa of whether vitamin D was included as part of the recommendations in the immigrant's guidelines.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Immigrants population including refugees and asylum seekers

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Clinical Practice Guidelines that focus on vitamin d and Clinical Practice Guidelines which focus on immigrants health

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be

stated.

Only Clinical Practice Guidelines

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Clinical Practice Guidelines that are related to vitamin D or to immigrants health

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Quality of clinical practice guidelines according to AGREE II scoring

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Recommendations for vitamin D in immigrants' guidelines

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

AGREE II instrument. Any disagreement will be resolved by discussion to reach a consensusTwo reviewers will independently evaluate the methodological quality of the included guidelines using

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Two reviewers will independently assess the guidelines according to the AGREE II tool.The following six domains of the AGREE II tool will be evaluated: Scope and Purpose, Stakeholder

Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Descriptive statistical analysis will be used for comparisons.

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 26.0 will be used for data analysis

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Not applicable

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery

No

Synthesis of qualitative studies
No

Systematic review
No

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological

No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Canada

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

Not applicable

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Not applicable

Add web link to the published protocol.

Not applicable

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

PhD thesis and a peer-review publication

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Vitamin D's clinical practice guideline

Immigrant's clinical practice guideline

AGREE II

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Not applicable

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Systematic Reviews

PROTOCOL

Open Access

Assessment of the quality and content of clinical practice guidelines (CPGs) for vitamin D and for immigrants using the AGREE-II instrument: a protocol for systematic review

Said Yousef[1,2*], Lamia Hayawi[3], Douglas Manuel[4,5,6], Ian Colman[1], Manny Papadimitropoulos[7,8], Alomgir Hossain[1,5], Moez Allslam Faris[9] and George A. Wells[1,2]

Abstract

Introduction: Worldwide, more immigrants experience vitamin D (vitD) deficiency than non-immigrants, which is attributed to ethnic variations, place or region of birth, skin pigmentation, clothing style, and resettlement-related changes in diet, physical activity, and sun exposure. Current recommendations in clinical practice guidelines (CPGs) concerning vitD are inadequate to address vitD deficiency among immigrants. CPGs may also lack guidance for physicians on vitD supplementation for immigrants. Moreover, there are concerns about the overall quality of these CPGs.

Objectives: This systematic review will collate and critically appraise CPGs relevant to immigrants' health and vitD. Moreover, we will evaluate whether the CPGs of vitD including recommendations for immigrants and clarify whether the CPGs of immigrants include recommendations on vitD.

Methods: A systematic search of Ovid MEDLINE® ALL, EMBASE, and Turning Research Into Practice (TRIP) electronic databases, guideline repositories, and gray literature will be conducted to identify relevant CPGs. Two reviewers will independently evaluate the methodological quality of the retrieved guidelines using the Appraisal of Guidelines, Research, and Evaluation-II (AGREE-II) instrument. CPGs scoring ≥60% in at least four domains, including "rigor of development," will be considered high quality.

Conclusion: Evaluating the quality and content of relevant CPGs may support researchers in developing national and global guidelines for immigrants. Furthermore, it may support vitD testing, nutritional counseling, and supplementation for vulnerable immigrant sub-populations.

Systematic review registration: PROSPERO CRD42021240562.

Keywords: Vitamin D, Clinical practice guideline, Immigrants, AGREE-II

Introduction

Globally, immigrant populations represent diverse categories including economic migrants, family members, refugees, and asylum [1, 2]. Immigrants' health status after immigration remains an important area of concern [3, 4]. Studies have shown that immigrants' physical and mental health declines quickly after arrival to their host countries [1, 4–6], and further health changes

*Correspondence: **Said Yousef**

[2] Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Room H1281, 40 Ruskin Street, Ottawa, ON K1Y4W7, Canada
Full list of author information is available at the end of the article

can occur over 5–10 years [4, 7]. Recent migrants are reported to have better health compared with people of the host country, including long-term migrants who had migrated to the host country at an earlier time; this phenomenon is called the "healthy immigrant effect" [8]. It has been hypothesized that the healthy immigrant effect results from a combination of pre- and post-migration factors. Pre-migration factors include biased and rigorous selection criteria that favor immigrants that are healthier, wealthier, and better educated than the general population in the country of origin [8, 9]. In addition, a decline in immigrants' health status after arrival may be explained by psychosocial factors and lifestyle changes [9–11]. The mechanisms underlying this health decline in immigrants have not been explicitly identified [4]. However, the healthy immigrant effect appears to decline over time when immigrants are exposed to their new environment [5]. Evidence also suggests that immigrants have lower vitD compared with native-born populations [12–14]. In a recent national large-scale Canadian data, ethnicity was found the most strongly associated factor with serum vitD status among immigrants from 153 countries and more than 13 ethnicities [14]. Moreover, vitD status varies among immigrants because of skin pigmentation, clothing, place or region of birth, and resettlement changes in diet, physical activity, and sun exposure [12, 14–16].

The Institute of Medicine (IOM) defines clinical practice guidelines (CPGs) as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [17]. The main purposes of CPGs are to improve the effectiveness and quality of care and decrease variations in healthcare practices based on scientific evidence [17, 18]. Worldwide, more CPGs covering immigrants' health have become available in the last two decades, with the main focus areas being screening, treatment, immunization, infectious diseases, mental health, and chronic diseases [2, 19, 20]. The Canadian Immigrant and Refugee Guideline refers to the first 5 years of immigration to Canada as the time during which the healthy immigrant effect begins to decline. However, the developers of this guideline highlighted the topic of vitD deficiency among immigrants as an emerging condition that was not emphasized in their guidelines [20].

CPGs covering vitD that are currently available vary among countries and professional development organizations in terms of the scope, targeted population, and recommendations [21–24]. Notably, the current recommendations for vitD are inadequate to address the growing epidemic of vitD deficiency in immigrant populations [23, 25]. Moreover, the majority of guidelines do not include specific recommendations for different immigrant populations or certain ethnic groups [21, 23, 26, 27].

In addition, concerns have been raised about the overall quality of these CPGs [2, 28, 29]. The Appraisal of Guidelines for Research and Evaluation-II (AGREE-II) instrument has been widely used to assess guideline quality, define the information that needs to be reported, and inform guideline development [30, 31]. The overall guideline assessment includes judgment on the quality of the guideline and whether the guideline would be recommended for use [31]. Previous studies that assessed the quality of CPGs using the AGREE-II instrument were inconsistent in how they determined high quality. For example, with the inclusion of the "rigor of development" domain, a score of high quality was reported as ≥60% in at least three of the six domains [2], four of the six domains [32], or in all six domains [33].

Research objectives

This systematic review will focus on the critical appraisal of guidelines relevant to vitD and immigrants' health using the AGREE-II instrument. Moreover, it aims to evaluate the guideline content to clarify whether recommendations for immigrant populations were included in vitD guidelines and whether vitD recommendations were included in immigrant guidelines.

Research questions

The appraisal will be based on specific research questions and clarify whether the included CPGs comply with the quality standards of the AGREE-II instrument. The research questions are as follows: "Do immigrant CPGs include recommendations on vitD?" and "Do vitD CPGs include recommendations for immigrants, including refugees and asylum seekers?"

Methods and study design

The protocol for this review was registered with PROSPERO (CRD42021240562) [34]. The review procedures will follow the methods outlined in the Cochrane Handbook for Systematic Reviews [35]. This protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) Statement [36]; the checklist is presented in Additional file 1.

Search strategy

The search strategy used to identify published CPGs covering immigrants and vitD will be developed in consultation with an experienced medical information specialist. The databases searched will include Ovid MEDLINE® ALL and EMBASE. These searches will use a combination of controlled vocabulary (e.g., "VitD," "emigrants

and immigrants," "refugees") and keywords (e.g., "vitD," "asylum seeker," "foreigner") and incorporate a CADTH-derived guideline filter. The Ovid MEDLINE search strategy is presented in Additional file 2.

We will also search the Turning Research Into Practice (TRIP) database. In addition, we will search gray literature for guidelines that were internally produced by governments, organizations, and academic institutions and that publishing is a secondary activity for these organizations. For example, a search in the Guidelines International Network (GIN), Joanna Briggs Institute (JBI), World Health Organization (WHO), Healthcare Research and Quality (AHRQ), and National Institution for Excellence (NICE) will be conducted. Results will be limited to relevant publications between 2010 and the date of the search. Supplemental searching will be performed on the reference lists of identified CPGs to detect other key articles.

Eligibility criteria

We will include two types of CPGs: those concerning immigrants' health and those concerning vitD. The included guidelines will conform to the IOM definition of CPGs [17] and must have been published in the English language between 2010 and the search date. We will include CPGs that have recommendations intended for healthcare professionals on screening, diagnosis, management, or treatment related to immigrants' health or vitD. No restrictions will be applied in regard to age, sex, or health status. In this review, we will define immigrants as those who move cross-country or are international migrants residing in a destination country, irrespective of legal status and generation. Therefore, any CPGs that include immigrants as a primary population will be evaluated using the AGREE-II tool. CPGs for vitD that emphasizes care for patients who are at risk for vitD deficiency in terms of evaluation, treatment, and prevention will also be evaluated using the AGREE-II tool.

Exclusion criteria

We will exclude non-English language guidelines or incomplete texts. We will also exclude healthcare guidelines that do not consider immigrants or vitD as the primary objective. Dietary or nutritional guidelines for vitD that are not intended for healthcare practices or that target the general population will also be excluded. Furthermore, we will exclude position and consensus papers as well as any other documents that are not equivalent to guidelines.

Outcomes

The primary outcome of this review will be the quality score of the included CPGs based on the AGREE-II scoring tool. Secondary outcomes will be recommendations on vitD as part of immigrant guidelines and recommendations in vitD guidelines that target immigrants.

Selection of CPGs and data extraction

The systematic review software "Covidence" (www.covidence.org) will be used to remove duplicates and screen the titles and abstracts of identified GPGs. We will use the AGREE-II instrument (https://www.agreetrust.org) to evaluate the quality of the included guidelines. This tool comprises 23 items and evaluates six domains: "scope and purpose," "stakeholder involvement," "rigor of development," "clarity of presentation," "applicability," and "editorial independence" [31]. An electronic standardized form will be used to record these data and individual items will be rated using a seven-point Likert scale (1 = strongly disagree, 7 = strongly agree) [31]. More details are available in the AGREE-II manual [31]. The AGREE-II scoring sheet is presented in Additional file 3.

Two reviewers (SY and LH) will independently follow the inclusion and exclusion criteria to assess the citations for inclusion. Both reviewers will resolve differences in their decisions through discussion. A consultation with a third reviewer will be counted when a consensus cannot be reached.

One reviewer (SY) will extract the main characteristics of the included published guidelines, including the title, author(s) name(s), year of publication, country, and organization that produced the guideline, and key recommendations related to immigrants in vitD CPGs or vitD in immigrant CPGs. The extracted data will be checked by a second reviewer.

Following the application of the inclusion and exclusion criteria, two reviewers (SY and LH) will independently evaluate the methodological quality of the included guidelines. Both reviewers had previous training in using the online AGREE-II, and the resulting study was published [32]. Any disagreements will be resolved by discussion with a third reviewer to reach a consensus. The reviewers will evaluate the content of each CPG, and any additional supporting documents that are cited in the published guidelines.

Quality evaluation and data synthesis

The reviewers' decisions on the overall quality of recommendations contained in the guidelines will be based on the context in which the AGREE-II is being used. The mean scores for each AGREE-II domain and the overall quality will be presented. A standardized score for each domain will be calculated using the formula: ((actual score—minimum score)/(maximum score—minimum score)) × 100% [37].

CPGs that score ≥60% in at least four of the six domains, including the "rigor of development" domain, will be considered high quality [32, 38–40]. The intra-class correlation coefficient (ICC) and 95% confidence intervals will be calculated to assess the overall agreement between the reviewers for each guideline. The ICC will be classified as poor (<0.40), moderate (0.40–0.59), good (0.60–0.74), or excellent (0.75–1.00) based on a previous study [41]. We will analyze and summarize the extracted data in a tabular and narrative format. The characteristics of the identified CPGs including author, year, and country with the title will be presented in a table and quality assessment information like the domain percentage score, the ICC, and the overall quality of each guideline in another table. We will narratively discuss if immigrants or ethnicity was mentioned in the guidelines of VitD. Similarly, we will narratively discuss if vitD D was mentioned in CPGs for immigrants.

Discussion

Current national immigrant health policies only cover fragmented snapshots of global immigrant health. In response to growing issues related to immigrants' health, previous researchers recommended regional or global health-related protection agreements [42]. Furthermore, researchers recommended developing a global immigrant guideline that specifies sub-populations for which the evidence and recommendations may differ from the overall immigrant population [12, 43]. For example, the Endocrine Society guidelines recommend screening African Americans, Hispanic Americans [44], and all refugees for vitD deficiency [45]. In a recent Canadian national survey analysis, Yousef et al. (2021) reported vitD levels among immigrants from 153 origins and more than 13 ethnic groups. That study reported vitD deficiency attributable to ethnicity or country of birth was 6.6–62.1%, with the highest deficiency levels in the Japanese, Arab, and Southeast Asian ethnic groups, and among those born in Morocco, India, and Lebanon [14].

In this review, evaluating the quality and reviewing the content of the guidelines in terms of the recommendations for vitD and immigrants may support researchers in developing national and global immigrant guidelines. VitD-related recommendations may differ for sub-populations who are at high risk for vitD deficiency. Moreover, this review may also help and guide clinicians to support specific vitD testing, nutritional counseling, and supplementation for vulnerable immigrant sub-groups.

Abbreviations

AGREE-II: Appraisal of Guidelines, Research, and Evaluation II instrument; CPGs: Clinical practice guidelines; VitD: Vitamin D; IOM: Institute of Medicine; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol; CADTH: Canadian Agency For Drugs And Technologies In Health; TRIP: Turning Research Into Practice; ICC: Intra-class correlation coefficient.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-022-02129-6.

Additional file 1. PRISMA-P checklist-Vit D Yousef et al..

Additional file 2. Ovid Medline CPGs.

Additional file 3. AGREE-II Checklist.

Acknowledgements

We thank Sarah Visintini, MLIS (Berkman Library, University of Ottawa Heart Institute), and Becky Skidmore, MLS, Ottawa, ON, for a peer review of the MEDLINE search strategy.

Authors' contributions

YS, HL, MD, CI, PM, HA, FM, and GW conceived this study. YS designed and will execute the search strategy. YS and HL will screen, select studies for inclusion, and perform data extraction. YS drafted the protocol, which was revised by all authors. The authors have approved the version of the manuscript submitted for publication.

Funding

No funding was received for this study.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada. [2]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Room H1281, 40 Ruskin Street, Ottawa, ON K1Y4W7, Canada. [3]Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada. [4]Ottawa Hospital Research Institute, Ottawa, Canada. [5]Institute for Clinical Evaluative Sciences, Ottawa, Canada. [6]Department of Family Medicine, University of Ottawa, Ottawa, Canada. [7]Eli Lilly Canada Inc., Toronto, Canada. [8]Faculty of Pharmacy, University of Toronto, Toronto, Canada. [9]Department of Clinical Nutrition and Dietetics, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, UAE.

Received: 4 September 2021 Accepted: 8 November 2022
Published online: 17 November 2022

References

1. Health Canada. Canadian research on immigration and health: Heal Canada; 1999. https://publications.gc.ca/collections/Collection/H21-149-1999E.pdf.
2. Agbata EN, et al. Migrant healthcare guidelines: a systematic quality assessment. J Immigr Minor Health. 2019;21(2):401–13.
3. Fernando G. De Maio and Eagan Kemp, The deterioration of health status among immigrants to Canada: EBSCOhost, *Vol. 5, No. 5, September 2010,*

462478, 2010. [Online]. Available: http://web.a.ebscohost.com.proxy.bib.uottawa.ca/ehost/pdfviewer/pdfviewer?sid=31655445-ec33-4cb7-b2b5-dc5b315f7237%40sessionmgr4007&vid=1&hid=4206.
4. Newbold B. The short-term health of Canada's new immigrant arrivals: evidence from LSIC. Ethn Health. 2009;14(3):315–36.
5. Kennedy S, Mcdonald JT, Biddle N. The healthy immigrant effect and immigrant selection: evidence from four countries; 2006.
6. E. Hansson, A. Tuck, S. Lurie, and K. McKenzie, Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement, *for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada*, 2010. [Online]. Available: http://www.mentalhealthcommission.ca/SiteCollectionDocuments/Key_Documents/en/2010/Issues_Options_FINAL_English 12Nov09.pdf. (Accessed: 28 Nov 2016).
7. Newbold B. Health status and health care of immigrants in Canada: a longitudinal analysis. J Heal Serv Res Policy Nurs Allied Heal Database pg. 2005;10(2):77-83.
8. Ichou M, Wallace M. The healthy immigrant effect: the role of educational selectivity in the good health of migrants. Demogr Res. 2019;40:61–94.
9. Chiu M, Austin PC, Manuel DG, Tu JV. Cardiovascular risk factor profiles of recent immigrants vs long-term residents of Ontario: a multi-ethnic study. CJCA. 2012;28:20–6.
10. Morton B. The International refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada; 1993.
11. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci. 2010;1186(1):69–101.
12. Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: a meta-analysis. Nutrition. 2016;32:21–32.
13. Spiro A, Buttriss JL. Vitamin D: an overview of vitamin D status and intake in Europe. Nutr Bull. 2014;39(4):322–50.
14. Yousef S, et al. Vitamin D status among first-generation immigrants from different ethnic groups and origins: an observational study using the Canadian Health Measures Survey. Nutr 2021. 2021;13(8):2702.
15. Centers for Disease Control and Prevention, Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination division of global migration and quarantine, 2013.
16. Granlund L, Ramnemark A, Andersson C, Lindkvist M, Fhärm E, Norberg M. Prevalence of Vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden. Eur J Clin Nutr. 2016;70(3):373–9.
17. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E. Clinical Practice Guidelines We Can Trust; 2011.
18. Kredo T, et al. Guide to clinical practice guidelines: the current state of play. International J Qual Health Care. 2016;28(1):122.
19. Swinkels H, Pottie K, Tugwell P, Rashid M, Narasiah L, C. C. for I. and R. H. Canadian Collaboration for Immigrant and Refugee Health (CCIRH), Development of guidelines for recently arrived immigrants and refugees to Canada: delphi consensus on selecting preventable and treatable conditions. CMAJ. 2011;183(12):E928–32.
20. Pottie K, Greenaway C, Feightner J, Welch V, Swinkels H, Rashid M, Narasiah L, et al. Evidence-based clinical guidelines for immigrants and refugees. CMAJ. 2011;183(12):E824-925.
21. Rusinska A, et al. Vitamin D supplementation guidelines for general population and groups at risk of vitamin D deficiency in Poland-Recommendations of the Polish society of pediatric endocrinology and diabetes and the expert panel with participation of national specialist consultants and representatives of scientific societies-2018 update. Front Endocrinol. 2018;9(246):1–21.
22. National Institute for Health and Care Excellence. Vitamin D: supplement use in specific population groups, vol. 2014; 2014. p. 1–54.
23. Alberta Medical Association. Toward Optimized Practice (TOP) Working Group for Vitamin D. Guideline for vitamin D testing and supplementation in adults. Edmonton: Toward Optimized Practice; 2012.
24. Dai Z, et al. Methodological quality of public health guideline recommendations on vitamin D and calcium: a systematic review protocol. BMJ Open. 2019;9(11):e031840.
25. Ginde AA, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med. 2009;169(6):626–32.
26. M. of H. and L.-T. C. Government of Ontario, Clinical utility of vitamin D testing an evidence-based analysis medical advisory secretariat ministry of health and long-term care how to obtain issues in the Ontario Health Technology Assessment Series Conflict of Interest Statement, *Ontario Heal*. Technol Assess Ser Ont Heal. 2010;10(102):1–95 Feb [cited YYYY MM DD].
27. Ministry of Health-British Columbia, B.C. guidelines and protocols advisory committee. Vitamin D testing protocol, 2010.
28. S. Pilz *et al.*, Vitamin D testing and treatment: a narrative review of current evidence, 2019.
29. Hanley DA, et al. Vitamin D in adult health and disease: a review and guideline statement from osteoporosis Canada. Cmaj. 2010;182(12):1–9.
30. Brouwers MC, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. C C • JUL. 2010;13(10):182.
31. M. C. Brouwers *et al.*, Appraisal Of Guidelines For Research & Evaluation II, 2017.
32. Hayawi LM, Graham ID, Tugwell P, Abdelrazeq SY. Screening for osteoporosis: a systematic assessment of the quality and content of clinical practice guidelines, using the AGREE II instrument and the IOM Standards for Trustworthy Guidelines; 2018.
33. Zhou X, Xu S, Ren Q, Chen J. Quality and specific concerns of clinical guidelines for integrated Chinese and Western medicine: a critical appraisal. Evid-based Complement Altern Med. 2020;2020:1-11.
34. S. Yousef, L. M. Hayawi, and G. A. Wells, A systematic assessment of the quality and the content of the immigrant's health and vitamin D's clinical practice guidelines (CPGs) using the AGREE II instrument, *PROSPERO #CRD42021240562*, May-2021. [Online]. Available: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=240562. (Accessed: 14 Jul 2021).
35. G. S. (editors). Higgins JPT, Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. 2011.
36. Moher D, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
37. Brouwers MC. Appraisal of guidelines for research & evaluation II -agree next steps consortium membership; 2009.
38. Armstrong JJ, Rodrigues IB, Wasiuta T, Macdermid JC. Quality assessment of osteoporosis clinical practice guidelines for physical activity and safe movement: an AGREE II appraisal. Arch Osteoporos. 2016;1-10.
39. Font-Gonzalez A, et al. Fertility preservation in children, adolescents, and young adults with cancer: quality of clinical practice guidelines and variations in recommendations. Cancer. 2016;122(14):2216–23.
40. Ou Y, Goldberg I, Migdal C, Lee PP. A critical appraisal and comparison of the quality and recommendations of glaucoma clinical practice guidelines. Ophthalmology. 2011;118:1017–23.
41. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess. 1994;4:284–90.
42. Zimmerman C, Kiss L, Hossain M. Migration and health: a framework for 21st century policy-making. PLoS Med. 2011;8(5):1–7.
43. Yousef S, et al. Study protocol: worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations - a systematic review and meta-analysis. Syst Rev. 2019;8(1):1-6.
44. Holick MF, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
45. Benson J, Skull S. Hiding from the sun - vitamin D deficiency in refugees. Aust Fam Physician. 2007;36(5):355-7. PMID: 17492073.

Publisher's Note

Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis

Said Yousef Abdelrazeq, George A. Wells, Jesse Elliott

Citation

Said Yousef Abdelrazeq, George A. Wells, Jesse Elliott. Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis. PROSPERO 2018 CRD42018086729 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018086729

Review question

A. Are vitamin D levels lower among immigrants compared to local populations?

B. Are vitamin D levels different between the same ethnic groups of immigrants in different regions worldwide?

C. Are immigrants at a higher risk of vitamin D related-chronic diseases compared to local populations?

Searches

The search strategy will include the following databases: EMBASE (Ovid) Cochrane Library (Wiley), and PubMed for the publications that are not part of MEDLINE. As well as, Web of Science and Dissertations and Theses Global (ProQuest) for theses, conference proceeding, and other grey literature will be searched. The international and governmental websites such as Research Data Centre, WHO, Canadian Institute for Health Information (CIHI), and National Institute for Health Care Excellence (NICE) will be searched.

Supplemental searching will be performed searching for key articles using the reference citation.

No studies will be excluded based on language, date, reported outcomes, and comparators.

Types of study to be included

Inclusion: all study designs will be eligible for inclusion except case reports, case series, systematic or narrative reviews, editorials, commentaries, and letters.

Studies involving participants of all age groups for whom immigration status has been reported and defined as foreign-born (immigrants of first generation) will be included.

Exclusion: studies involving populations at higher risk of vitamin D deficiency, such as those with chronic illnesses, will be excluded.

Studies also will be excluded from the analysis if the concentration levels of vitamin D has not been reported for the immigrant population.

Condition or domain being studied

Immigrants worldwide have lower vitamin D levels due to the changes in the lifestyle, dietary habits, physical activity, physical and social environment, and other socio-demographic characteristics.

Migration is a risk factor for vitamin D deficiency. Migration of people from sunny countries to a more northerly latitude increases the risk of vitamin D deficiency due to less ultraviolet light during the harsh snowy

weather and long winter seasons. The majority of recent immigrants are darker skin and low socioeconomic status which makes them potentially at high risk of vitamin D deficiency; changes in their lifestyle, physical activities, and nutrition habits in the new country are factors.

Participants/population

Participants of all age groups for whom immigration status has been reported and defined as foreign-born (immigrants of first generation).

Populations at higher risk of vitamin D deficiency, such as those with chronic illnesses, will be excluded.

The concentration levels of vitamin D must have been reported for the immigrant population.

Intervention(s), exposure(s)

Immigration is the exposure, in which migration is a risk factor for vitamin D deficency.

Comparator(s)/control

Non-immigrants (populations of a host country, e.g., Canadian populations, defined as having been born in Canada).

Context

Main outcome(s)

- Vitamin D deficiency.

- The mean of vitamin D (25(OH)D) levels will be used to define deficient or insufficient vitamin D.

Additional outcome(s)

Vitamin D deficiency-related disease status (e.g., cardiovascular, diabetes, cancer, osteoporosis, depression, chronic pain, and respiratory infections).

Data extraction (selection and coding)

All studies will be independently screened and evaluated for selection by two reviewers, and any disagreements will be discussed and resolved by consensus.

One reviewer will extract the data from the included studies, which will be double-checked by the second reviewer.

Risk of bias (quality) assessment

The quality of the included studies will be assessed using the Cochrane Collaboration’s risk of bias tool (ROB v. 2.0) for RCTs, and the Risk Of Bias in Non-Randomized Studies of Exposure (ROBINS-E). The Joanna Briggs tool will be used for single-arm cohorts.

Strategy for data synthesis

There will be three approaches for data synthesis:

1- All immigrants to a given country will be compared with that country's local population (pooling all immigrant data of all origins).

2- Compare same ethnic group of immigrants in different geographical regions worldwide.

3- Vitamin D related disease status will be compared between immigrants and non-immigrants.

Standardized and piloted forms for data extraction will be used to extract the characteristics of the studies and participants, as well as the specific details from each study (e.g., mean or median of vitamin D

concentration levels, ethnicity, country of birth or origin, and the host country). Data for all immigrants and a priori defined subgroups will be extracted. The study outcomes will be narratively summarized in a tabular format and pooled via meta-analysis, based on the availability of the data taking into account the clinical and methodological heterogeneities of the included studies.

Descriptive statistics will be implemented for the baseline features of the included studies. The mean and/or the median of the concentration levels of vitamin D will be used to compare immigrants to non-immigrants. The continuous values will be used to identify the status of vitamin D (adequate, insufficient and deficient by using the cut-off of >75 nmol/l, ? 50 nmol/l, and ? 30 nmol/l respectively as described by the Institute of Medicine). When the concentration level of vitamin D is given as ng/mL, it will be multiplied by 2.496 to attain the nmol/L. The heterogeneity between the included studies will be visually evaluated by assessment of forest plots and analytically evaluated by the calculation of I^2 statistics.

Analysis of subgroups or subsets

Subgroup analyses will be performed based on the geographical regions in which immigrants have resettled, the age groups of the participants, their immigration status (refugees, and other classes) and the number of years since immigration (long-term and short-term immigrants).

Contact details for further information
Said Yousef

Organisational affiliation of the review
School of Epidemiology and Public Health, University of Ottawa

Review team members and their organisational affiliations
Mr Said Yousef Abdelrazeq. School of Epidemiology and Public Health, University of Ottawa
Dr George A. Wells. University of Ottawa-Heart Institute
Ms Jesse Elliott. School of Epidemiology and Public Health, University of Ottawa

Anticipated or actual start date
15 June 2018

Anticipated completion date
31 December 2019

Funding sources/sponsors
School of Epidemiology and Public Health, student research support

Conflicts of interest
None known

Language
English

Country
Canada

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Emigrants and Immigrants; Emigration and Immigration; Healthcare Disparities; Health Status; Health Status

Disparities; Humans; Malnutrition; Nutritional Status; Risk Factors; Vitamin D; Vitamin D Deficiency

Date of registration in PROSPERO
16 July 2018

Date of publication of this version
22 November 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
16 July 2018
29 October 2018
22 November 2018

Yousef et al. Systematic Reviews (2019) 8:211
https://doi.org/10.1186/s13643-019-1123-4

Systematic Reviews

PROTOCOL Open Access

Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations—a systematic review and meta-analysis

Said Yousef[1,2*], Jesse Elliott[1,2], Douglas Manuel[3,4,5], Ian Colman[1,6], Manny Papadimitropoulos[7,8], Alomgir Hossain[1,4], Nathalie Leclair[9] and George A. Wells[1,2]

Abstract

Background: A growing body of literature indicates that, worldwide, immigrants experience health deterioration after their arrival into their adopted country, and moreover, they have lower vitamin D compared to the native-born population. We plan to review if the levels of vitamin D are comparable between different ethnic groups in different regions of the world with those of native-born populations and to identify the possible associations between vitamin D deficiency and disease status among immigrants.

Methods/design: A systematic review and meta-analysis will be conducted following the methods of the Cochrane handbook for systematic reviews. A literature search was performed to identify studies on immigrants and vitamin D. The primary outcome is vitamin D levels, and the secondary outcome is any vitamin D deficiency-related disease. Study design and participant characteristics will be extracted, including ethnicity, country of birth and/or origin, and the host country. Descriptive and meta-analytic summaries of the outcomes will be derived. Distiller-SR and RevMan will be used respectively for data management and meta-analysis.

Discussion: This systematic review may partially help clarify vitamin D-related health deterioration in migrants; moreover, to develop a global guideline that specifies sub-populations, in which the evidence and vitamin D-related recommendations might differ from the overall immigrant population.

Systematic review registration: PROSPERO CRD42018086729

Keywords: Systematic review, Meta-analysis, Vitamin D, Immigrants' health deterioration

Background

Healthy people are more likely to migrate, and those with serious medical conditions may be disqualified [1, 2]. Despite particular groups, such as refugees, who are not as healthy as other immigrants, substantial evidence indicates that the health of immigrants at the time of arrival is significantly better than the health of the native-born population of the host country [3–8]. Recent studies have shown that the physical and mental health of immigrants declines after their arrival into the adopted country [2, 4, 8–12], and health changes can occur within 5 to 10 years [9, 13–15]. Migration studies suggest that the integration process is likely a new experience for immigrants, in which changes in the environment and lifestyle are well-documented factors predisposing migrants to chronic diseases [8, 16, 17]. Moreover, migration experience and post-migration integrations are believed to explain the decline in the health status of immigrants [4, 11, 18]. However, the mechanistic reasons

* Correspondence: Said Yousef

[1]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

[2]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada

Full list of author information is available at the end of the article

underlying the decline in immigrants' health have not been explicitly identified [4, 14]. Worldwide research evidence suggests that migration is a significant risk factor for low vitamin D levels due to resettlement changes in lifestyle and sun exposure [19–22]. Vitamin D plays a crucial role in physiological functions; it regulates the absorption of calcium and phosphorus that support both skeletal (bone hemostasis) and non-skeletal health [23, 24].

The dietary sources for vitamin D are plant-based foods (e.g., mushroom) which include vitamin D2 (ergocalciferol) and the animal-based foods (e.g., salmon and tuna fish) which include vitamin D3 (cholecalciferol) [21, 25]. In addition to the natural food-based sources, the human body obtains vitamin D from artificial sources such as supplements and fortified food. The primary source, however, is through skin exposure to the sunlight (cutaneous synthesis of vitamin D) [26], and therefore, vitamin D is commonly known as the 'sunshine vitamin' because the body can make it through exposure to sunlight whereas most other vitamins are food-based ingestion [27]. However, the ability of body to create and maintain sufficient levels affected by socio-demographic factors (e.g., socioeconomic status, age, and gender), geographical and environmental factors (e.g., season and the latitude), cultural and religious factors (e.g., clothing, sedentary behaviors and prolonged breastfeeding time), lifestyle and dietary factors (e.g., vegetarian diet), as well as genetic and health factors (e.g., skin pigmentation and obesity) [20, 23, 28–30]. A study on people from different ethnic origin who have similar practices proposes that skin pigmentation is possibly the most significant risk factor for vitamin D deficiency irrespective of the ultraviolet light exposure [31].

The concentration of 25-hydroxyvitamin D serum (25(OH)D) represents the combined contributions of the cutaneous synthesis and the dietary intake of vitamin D and is considered the best clinical indicator for the overall adequacy of vitamin D [23, 25, 27]. There is no international agreement regarding the reference range for serum 25(OH) D concentrations. The Institute of Medicine (IOM) has developed different categories for the concentration levels of the serum 25(OH)D in blood, which include optimal (> 75 nmol/l), sufficient (> 50 nmol/l), inadequate or deficient (≤ 50 nmol\l), and deficient (< 30 nmol/l) levels [27]. According to the World Health Organization, the levels of serum 25(OH)D below 50 nmol/l were classified as insufficient and levels below 25 nmol/l were considered as deficient [32].

Vitamin D deficiency is a global pandemic health problem in all age groups that occurs in countries with both high and low levels of sunlight (degree of the latitudes) [23, 24]. Hilger et al. in a systematic review of studies from 44 countries with data from 112 articles (168,389 participants), reported a wide range of serum 25(OH)D between 4.9 and 136.2 nmol/l with age and sex variations. Mean levels of < 50 nmol/l were reported in one third of these studies [33]. The highest levels of serum 25(OH)D were among participants who live in North America while those who live in the Middle East and Africa regions have much lower levels [33].

Studies show that worldwide migrant populations, including refugees and asylum, have lower levels of vitamin D compared with the local populations [20, 30, 34]. Refugees are considered at particularly higher risk for vitamin D deficiency due to staying indoors to avoid dangers, cold weather, living in high-rise buildings that limit their outdoor activities and sun exposure, and concerns regarding skin cancer [20]. The age, ethnicity, country of origin, higher latitudes, nutritional barriers, cultural practices, and the length of time after immigration were reported in several studies as being associated with the risk of vitamin D deficiency among immigrants [20, 30, 36]. Migrants are often considered as low-SES individuals, and immigrants of low SES were found to have a higher risk of vitamin D deficiency [35], as well as to develop physical and mental illnesses [16, 30, 36].

Previous studies support the hypothesis that the inadequate or deficient level of vitamin D is associated with increased risk of all-cause mortality and a wide range of physical and mental health diseases, including osteoporosis, type 1 diabetes mellitus, cancer, cardiovascular disease, obesity, schizophrenia and depression, and the metabolic syndrome [17, 23, 33, 36–39].

Although there is disagreement about optimal levels of serum 25(OH)D, evidence suggests that levels < 30 nmol/l are associated with an increased risk of some diseases in which vitamin D deficiency has been found to play a role. Moreover, the thresholds for serum 25(OH)D may vary according to different outcomes and subgroups, and the most advantageous levels begin at 75 nmol/l [40–43].

The most relevant systematic review to this protocol published by Martin et al. 2016 has focused on dark skin immigrants including both first- and second-generation immigrants. Moreover, the included studies were selected from certain regions associated with dark skin, namely, Africa; West, South, Central, and Southeast Asia; the Middle East; the Caribbean, and Central America [20]. Whereas the current systematic review will include only the first-generation immigrants who were defined as foreign-born population and no geographical restrictions will be applied. However, to the best of our knowledge, no study has systematically reviewed the vitamin D deficiency-related diseases and immigrant status.

The aims of this systematic review and meta-analysis are the following: first is to compare the levels of vitamin D between ethnic groups of immigrants in different regions with those of native-born populations. Consequently, the findings will be used to establish global maps for vitamin D status of immigrants and non-immigrants, as well as maps

for the same ethnic immigrants (at high risk) in different geographical regions of the world. Second is to identify the possible associations between vitamin D deficiency and disease status among immigrants.

Methods/design

The protocol of this review has been registered on PROSPERO (CRD42018086729) [44]. The strategy involves a comprehensive systematic review of the literature and meta-analysis. The procedures will follow the methods outlined in the Cochrane handbook for systematic reviews [45]. This includes guidance in planning the review, searching and selecting studies, collecting data, as well as the risk of bias and prospective meta-analysis. The protocol of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) Statement [46]; the checklist is presented in Additional file 1.

Literature search

A systematic literature search was performed to identify studies on immigrants and vitamin D. The primary search strategy was completed in MEDLINE(R) ALL (Ovid) by a medical information specialist using a combination of subject headings and keywords. The strategy was peer-reviewed by an independent information specialist using the Peer Review of Electronic Search Strategies (PRESS) guidelines [47]. The final search strategy was run on August 16, 2018, and translated to EMBASE Classic + Embase (Ovid) (available in Additional file 2), PubMed, and Web of Science Indexes (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI) on the same day, and to Cochrane (Wiley on INSERT DATE). With regard to the grey literature, Dissertations and Theses Global (ProQuest) was searched as well as international and governmental websites, including the World Health Organization (WHO), the Canadian Institute for Health Information (CIHI), and the National Institute for Health Care Excellence (NICE). Supplemental searches will be performed using backward chaining (looking through the bibliographies of included studies for additional relevant articles).

Eligibility criteria and study selection

Two reviewers independently will follow the population, exposure, comparator, and outcomes (PECO) criteria in evaluating the included studies. The population of interest is immigrants, defined as foreign-born. The exposure is the integration process over time in the new environment after immigration, and the comparator is the non-immigrant (native-born population). The primary outcome is vitamin D levels, and the secondary outcome is any vitamin D deficiency-related disease (e.g., cardiovascular, diabetes, cancer, osteoporosis, depression, chronic pain, and respiratory infections).

All study designs will be eligible except the following publication types: case reports, case series, systematic or narrative reviews, editorials, and commentaries. Studies will be excluded if they do not define or include migrant status, including populations at higher risk for vitamin D deficiency such as chronic illness, and if the concentration levels of vitamin D are not reported. The publication with the largest sample size will be included if the same population is presented in more than one publication. No studies will be excluded from the search based on the language and the study date.

All studies will be independently screened and evaluated for eligibility by two reviewers, and any disagreement will be discussed and resolved by consensus.

Data extraction and synthesis

The data will be extracted by two independent reviewers. If necessary, discrepancies will be resolved through discussion [48]. Standardized and piloted forms for data extraction will be used to extract the characteristics of the studies and participants, as well as the specific details from each study (e.g., ethnicity, country of birth and/or origin, and the host country). Data for all immigrants and a priori defined subgroups will be extracted. Based on the availability, the mean and/or the median of the concentration levels of vitamin D will be summarized in a tabular format, pooled via meta-analysis, and used to compare immigrants to non-immigrants. Descriptive statistics will be implemented for the baseline features of the included studies. The vitamin D status will be identified based on the IOM categories (optimal, adequate, insufficient, or deficient) [27]. When the concentration level of vitamin D is given as nanograms per milliliter, it will be multiplied by 2.496 to attain the nanomoles per liter [49]. Participant and study characteristics of the included studies will be used to assess the clinical and methodological heterogeneity, respectively. The heterogeneity between the included studies will be completed through a visual assessment of forest plots and the calculation of the I^2 statistic, which provides a numerical summary of heterogeneity. The following categories of I^2 statistic will be considered: < 25%, 25 to 50%, and 50 to 75%. For I^2 > 50, heterogeneity will be explored using subgroup and meta-regression. If the reason for heterogeneity is identified, it will be reported accordingly. If heterogeneity is not resolved, the results will be pooled for I^2 between 50 and 75%, and a caveat regarding the heterogeneity will be provided. For I^2 > 75%, the results will not be pooled. Outcome data will be pooled using a random-effects model. Distiller SR and RevMan will be used to complete data extraction and meta-analyses, respectively.

Subgroup and sensitivity analysis

Depending on the availability and the quality of data (risk of bias), subgroup analysis will be conducted based on age, sex, ethnicity, country of birth and/or origin, geographical location and the latitude of the host country for immigrants, season, the immigration class (family, economic, and refugee classes), and the time since immigration.

Risk of bias and quality evaluation

The quality of the included studies will be assessed using the relevant tools depending on the study design. These tools may include Joanna Briggs, Scottish Intercollegiate Guidelines Network-Publication no.50 (SIGN50), Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E), as well as Cochrane Collaboration's Risk of Bias tool (ROB v. 2.0) [45, 50–52]. Two independent reviewers will evaluate the quality, and any disagreements between reviewers will be discussed and resolved by consensus.

Discussion

The baseline risk for vitamin D deficiency is higher among migrants especially those who have darker skin, such as Middle Eastern and African populations, and those who migrate from equatorial region to northern latitude [20, 33, 53]. Cultural and lifestyle practices that minimize sun exposure also increase the risk in these subgroups [20]. However, the developed recommendations for vitamin D supplementation provided in the Dietary Reference Intakes (DRIs) still inadequately address the growing epidemic of vitamin D insufficiency in immigrants and refugees [49]. For instance, the DRIs for vitamin D and calcium sets the recommended of daily intake assuming minimal sun exposure for all populations. Moreover, no additional recommendations are given for sub-populations such as immigrants living in high northern latitudes, those with darker skin pigmentation, or those who wear heavy clothing that inhibits sun exposure [54, 55]. In addition, most of the worldwide guidelines on vitamin D and/or immigrants' health does not entirely address these subpopulations in their recommendations [56–61].

Nonetheless, recent reviews recommended future studies to assess relevant data on vitamin D and determinants, including lifestyle factors with a subgroup comparison of the population within the same country [33], as well as further research specific to migrant populations to establish links between immigrant status and disease status [17]. Therefore, this systematic review may partially help to clarify vitamin D-related health deterioration in migrants and moreover, to develop a global guideline that specifies sub-populations, in which the evidence and recommendation might differ from the overall immigrant population.

Additional files

Additional file 1: Revised PRISMA-P checklist. (DOCX 39 kb)
Additional file 2: Search strategy. (DOCX 34 kb)

Abbreviations

25(OH)D: 25-Hydroxyvitamin D serum; A&HCI: Arts and Humanities Citation Index (1975–present); CIHI: Canadian Institute for Health Information; CPCI-S: Conference Proceedings Citation Index—Science (1990–present); CPCI-SSH: Conference Proceedings Citation Index—Social Science and Humanities (1990–present); DRIs: Dietary Reference Intakes; ESCI: Emerging Sources Citation Index (2005–present); IOM: Institute of Medicine; NICE: National Institute for Health Care Excellence; PECO: Population, Exposure, Comparator, and Outcomes; PRESS: Peer Review of Electronic Search Strategies; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol; ROB: Risk of bias tool; ROBINS-E: Risk Of Bias In Non-randomized Studies of Exposure; SCI-EXPANDED: Science Citation Index Expanded (1900–present); SIGN50: Scottish Intercollegiate Guidelines Network-Publication no. 50; SSCI: Social Sciences Citation Index (1900–present); WHO: World Health Organization

Acknowledgements

We thank Becky Skidmore, MLS, Ottawa, ON, for the peer review of the MEDLINE search strategy and subsequent translations to the other databases.

Authors' contributions

YS, MD, CI, PM, HA, and GW conceived the study. LN designed and executed the search strategy. YS and JE will screen, select the studies for inclusion, and perform the data extraction. YS drafted the protocol, which was revised by all authors. All authors have approved the version of the manuscript submitted for publication.

Funding

No funding

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada. [2]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada. [3]Ottawa Hospital Research Institute, Ottawa, ON, Canada. [4]Institute for Clinical Evaluative Sciences, Ottawa and Toronto, ON, Canada. [5]Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada. [6]Canadian Institutes of Health Research, Ottawa, ON, Canada. [7]Eli Lilly Canada Inc, Toronto, ON, Canada. [8]Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada. [9]Berkman Library, University of Ottawa Heart Institute, Ottawa, ON, Canada.

Received: 6 November 2018 Accepted: 26 July 2019
Published online: 22 August 2019

References

1. Laroche M. Health status and health services utilization of Canada's immigrant and non-immigrant populations. Can Public Policy. 2000;XXCI(1):51–73.
2. Solé-Auró A, Crimmins EM. Health of immigrants in European countries. Int Migr Rev. 2008;42(4). [cited 2018 Jul 31] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2967040/pdf/nihms220945.pdf
3. Chen J, Wilkins R, Ng E. Health expectancy by immigrant status, 1986 and 1991. Heal Rep. 1996;8(3):29–38.

4. Health Canada. Canadian Research on Immigration and Health. Health-Canada 1999;This publi. Available from: http://publications.gc.ca/site/eng/9.696347/publication.html
5. Pe'rez CE. Health status and health behaviour among immigrants [Canadian Community Health Survey - 2002 Annual Report] - ProQuest. Ottawa: Statistics Canada, 112, Catalogue 82-003-SIE; 2002. p. 89–100. Available from: https://www150.statcan.gc.ca/n1/en/pub/82-003-s/2002001/pdf/82-003-s2002005-eng.pdf?st=ERfZZ9Gx
6. Gee E, Kobayshi K, Prus S. Examining the "healthy immigrant effect"; in later life: findings from the Canadian Community Health Survey - ProQuest. 2003. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15660311
7. Dunn J, Dyck I. Social determinants of health in Canada's immigrant population: results from the national population health survey; 1998.
8. Hemminki K. Immigrant health, our health. Eur J Public Health. 2014 [cited 2018 Jul 31];24(suppl 1):92–5. Available from: https://academic.oup.com/eurpub/article-lookup/doi/10.1093/eurpub/cku108
9. Newbold B. Self-rated health within the Canadian immigrant population: risk and the healthy immigrant effect. Soc Sci Med. 2005;60:1359–70.
10. Kennedy S, Mcdonald JT, Biddle N. The healthy immigrant effect and immigrant selection: evidence from four countries. 2006 [cited 2016 Nov 26]; Available from: https://socialsciences.mcmaster.ca/sedap/papers06.htm
11. Williams DR, Mohammed SA, Leavell J, Collins C. Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci. 2010 [cited 2016 Nov 26];1186(1):69–101. Available from: http://doi.wiley.com/10.1111/j.1749-6632.2009.05339.x
12. Hansson E, Tuck A, Lurie S, McKenzie K. Improving mental health services for immigrant, refugee, ethno-cultural and racialized groups Issues and options for service improvement [Internet]. for the Task Group of the Services Systems Advisory Committee, Mental Health Commission of Canada. 2010 [cited 2016 Nov 28]. Available from: https://www.mentalhealthcommission.ca/sites/default/files/Diversity_Issues_Options_Report_ENG_0_1.pdf
13. Newbold B. Health status and health care of immigrants in Canada: a longitudinal analysis. J Heal Serv Res Policy Nurs Allied Heal Database pg. 2005;10:2.
14. Newbold B. The short-term health of Canada's new immigrant arrivals: evidence from LSIC. Ethn Health. 2009 [cited 2016 Nov 28];14(3):315–36. Available from: http://www.tandfonline.com/doi/abs/10.1080/13557850802609956
15. Zhao J, Xue L, Gilkinson T. Health status and social capital of recent immigrants in Canada. Policy Stud. 2010 [cited 2016 Nov 26];(March). Available from: http://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/collection_2015/cic/Ci4-139-2010-eng.pdf
16. Public Health Agency of Canada. Immigrant mental health. 2010 [cited 2017 Apr 10]; Available from: http://www.metropolis.net/pdfs/immigrant_mental_health_10aug10.pdf
17. Renzaho AM, Halliday BHSci JA, Nowson C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review. Nutrition. 2011 [cited 2018 Jan 22];27:868–79. Available from: https://www.sciencedirect.com/science/article/pii/S0899900711000128?via%3Dihub
18. Beiser Morton. The international refugee crisis : British and Canadian responses - CLIO. After the door has been opened: the mental health of immigrants and refugees in Canada. 1993. Available from: https://clio.columbia.edu/catalog/1176318
19. Granlund L, Ramnemark A, Andersson C, Lindkvist M, Fhärm E, Norberg M. Prevalence of vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden. Eur J Clin Nutr. 2015 [cited 2018 Jan 22];70(10):373–9. Available from: http://www.nature.com.proxy.bib.uottawa.ca/articles/ejcn2015176.pdf
20. Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. Nutrition. 2016 [cited 2018 Mar 19];32:21–32. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26643747
21. M.H. Edwards, Z.A. Cole, N.C. Harvey CC. The global epidemiology of vitamin D status. J Aging Rese Clin Pract. 2014 [cited 2018 Feb 9]. Available from: http://www.jarcp.com/703-the-global-epidemiology-of-vitamin-d-status.html
22. Holick MF. The vitamin D deficiency pandemic: a forgotten hormone important for health INTRODUCTION: HISTORICAL PERSPECTIVE. Public Health Rev. 2010 [cited 2018 Mar 29];32(1):267–83. Available from: https://publichealthreviews.biomedcentral.com/track/pdf/10.1007/BF03391602
23. Simon Spedding XZ, editor. Vitamin D and human health | MDPI Books. Edition 2015. Shu-Kun Lin; 2015 [cited 2018 Jan 23]. Available from: http://www.mdpi.com/books/pdfview/book/120
24. Wacker M, Holick MF. Vitamin D—effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013 [cited 2018 Mar 22];5:111–48. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571641/
25. Pham TT (Thesis for M. Vitamin D status of immigrant and ethnic minority children ages 2 to 5 y in Montréal. 2012 [cited 2018 Jan 7]; Available from: http://digitool.library.mcgill.ca/webclient/StreamGate?folder_id=0&dvs=1564852305581~524
26. Alshahrani AA, Alicia Garcia SC (Thesis for M degree). Vitamin D deficiency and possible risk factors among middle eastern university students in London, Ontario, Canada. 2014 [cited 2018 Jan 7]; Available from: http://ir.lib.uwo.ca/etd
27. Statistics Canada. Vitamin D blood levels of Canadians based on CHMS, cycle 2. 2015 [cited 2018 Mar 15]. Available from: http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm
28. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014 [cited 2018 Mar 28];144:138–45. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24239505
29. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009 [cited 2018 Mar 11];20(11):1807–20. Available from: http://link.springer.com/10.1007/s00198-009-0954-6
30. Centers for Disease Control and Prevention. Guidelines for evaluation of the nutritional status and growth in refugee children during the domestic medical screening examination division of global migration and quarantine. 2013 [cited 2018 May 6]; Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/Nutrition-and-Growth-Guidelines.pdf
31. Knoss R, Halsey LG, Reeves S. Ethnic Dress, vitamin D intake, and calcaneal bone health in young women in the United Kingdom. J Clin Densitom. 2012 [cited 2018 Aug 9];15(2):250–4. Available from: https://www.sciencedirect.com/science/article/pii/S1094695011001788?via%3Dihub
32. Rosen CJ. Clinical practice vitamin D insufficiency. Vol. 364, N Engl J Med. 2011 [cited 2019 Jun 21]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21247315
33. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. Br J Nutr. 2014 [cited 2018 Mar 11];111:23–45. Available from: https://www.cambridge.org/core/services/aop-cambridge-core/content/view/69657BC57AF7A214271655C5463F5293/S0007114513001840a.pdf/systematic_review_of_vitamin_d_status_in_populations_worldwide.pdf
34. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull. 2014 [cited 2018 Mar 28];39(4):322–50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288313/pdf/nbu0039-0322.pdf
35. Aucoin M, Dtmh C, Weaver R, Thomas R, Mrcgp C, Jones L, et al. Vitamin D status of refugees arriving in Canada Findings from the Calgary Refugee Health Program. 2013 [cited 2018 Jan 7];59. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625101/pdf/059e188.pdf
36. Gaksch M, Jorde R, Grimnes G, Joakimsen R, Schirmer H, Wilsgaard T, et al. Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. Zmijewski M, editor. PLoS One. 2017 [cited 2018 Mar 28];12(2):e0170791. Available from: http://dx.plos.org/10.1371/journal.pone.0170791
37. Dong J-Y, Zhang W, Chen J, Zhang Z-L, Han S-F, Qin L-Q. Vitamin D Intake and Risk of Type 1 Diabetes: A Meta-Analysis of Observational Studies. Nutrients. 2013 [cited 2018 Apr 1];5(9):3551–62. Available from: http://www.mdpi.com/2072-6643/5/9/3551
38. Chu F, Ohinmaa A, Klarenbach S, Wong Z-W, Veugelers P. Serum 25-Hydroxyvitamin D Concentrations and Indicators of Mental Health: An Analysis of the Canadian Health Measures Survey. Nutrients [Internet]. 2017 [cited 2018 Jan 10];9(10):1116. Available from: http://www.mdpi.com/2072-6643/9/10/1116
39. Huotari A, Herzig K-H. Vitamin D and living in northern latitudes—an endemic risk are for vitamin D defieciency. Int J Circumpolar Heal J Circumpolar Heal. 2008 [cited 2018 Feb 9];67(3). Available from: https://pdfs.semanticscholar.org/8daa/fce677c71dc430264f6acc253556dcd26c60.pdf
40. Heaney RP. Vitamin D in health and disease. Clin J Am Soc Nephrol. 2008 [cited 2019 Jun 21];3(5):1535–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18525006
41. Robyn Lucas & Rachel Neale. What is the optimal level of vitamin D? Separating the evidence from the rhetoric clinical. 2014 [cited 2019 Jun 21]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24600673

42. Sohl E, De Jongh RT, Heymans MW, Van Schoor NM, Lips P. Thresholds for serum 25(OH)D concentrations with respect to different outcomes. J Clin Endocrinol Metab. 2015 [cited 2019 Jun 21];100:2480–8. Available from: https://academic.oup.com/jcem/article-abstract/100/6/2480/2829682
43. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes 1-3. Vol. 84, Am J Clin Nutr. 2006 [cited 2019 Jun 21]. Available from: https://academic.oup.com/ajcn/article-abstract/84/1/18/4633029
44. Said Abdelrazeq, George A. Wells, Jesse Elliot SA. Worldwide comparison of vitamin D status in immigrants and local populations: a systematic review and meta-analysis [Internet]. PROSPERO. National Institute of Health Research; 2018 [cited 2018 Sep 6]. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018086729
45. Higgins JPT GS (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011; Available from: www.handbook.cochrane.org
46. Moher D, Stewart L, Shekelle P. Implementing PRISMA-P: recommendations for prospective authors. Syst Rev. 2016 [cited 2018 Sep 8];5(1):15. Available from: http://www.systematicreviewsjournal.com/content/5/1/15
47. Mcgowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 [cited 2018 Apr 4];75:40–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27005575
48. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 [cited 2018 Apr 9];4(1):1. Available from: http://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-4-1
49. Ginde AA, Liu MC, Camargo CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med. 2009 [cited 2018 Apr 4];169(6):626–632. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3447083/pdf/nihms-406918.pdf
50. SIGN 50: a guideline developer's handbook. [cited 2018 Oct 13]. Available from: https://www.sign.ac.uk/sign-50.html
51. University of Bristol. ROBINS-E|Bristol Medical School: Population Health Sciences | University of Bristol. [cited 2018 Oct 13]. Available from: https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/
52. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. [cited 2018 Oct 13]; Available from: https://academic.oup.com/ije/article-abstract/36/3/666/653571
53. Spedding S, Simon. Vitamin D and Human Health. 2015 [cited 2018 Mar 8]; Available from: https://www.mendeley.com/research-papers/vitamin-d-human-health/?utm_source=desktop&utm_medium=1.17.13&utm_campaign=open_catalog&userDocumentId=%7B25046fc3-571c-3be3-8c74-0692c572f659%7D
54. Government of Canada. Vitamin D and Calcium: Updated Dietary Reference Intakes - Canada.ca. Government of Canada website. 2012 [cited 2018 May 6]. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/vitamins-minerals/vitamin-calcium-updated-dietary-reference-intakes-nutrition.html#a5
55. Institute of Medicine. Dietary reference intakes for calcium and vitamin D health effects of vitamin D and calcium intake. 2011 [cited 2018 Jul 19]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK56070/
56. Pottie MCISc K, Greenaway C, Feightner J, Welch V, Swinkels MHSc H, Rashid M, et al. Evidence-based clinical guidelines for immigrants and refugees. E824 C. 2011 [cited 2018 Feb 25];(12). Available from: http://www.cmaj.ca/content/cmaj/183/12/E824.full.pdf
57. Government of Ontario M of H and L-TC. Clinical utility of vitamin D testing an evidence-based analysis medical advisory secretariat ministry of health and long-term care how to obtain issues in the Ontario Health Technology Assessment Series Conflict of Interest Statement. Ontario Heal Technol Assess Ser Ont Heal Technol Assess Ser. [cited YYYY MM DD [Internet]. 2010 [cited 2018 May 9];10(102):1–95. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23074397
58. Ministry of Health- British Columbia. B.C. Guidelines and Protocols Advisory Committee. Vitamin D Testing Protocol. 2010 [cited 2018 May 9]; Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/vitamind_summary.pdf
59. Alberta Medical Association. Toward optimized practice (TOP) working group for vitamin D. Guideline for vitamin D testing and supplementation in adults. Edmonton, AB: Toward Optimized Practice. 2012 [cited 2018 May 9]; Available from: http://www.topalbertadoctors.org/download/606/Guideline+for+Vitamin+D+Use+in+Adults+2012+October+31.pdf
60. The Royal Children's Hospital Melbourne. Clinical Practice Guidelines: Vitamin D deficiency. [cited 2018 Aug 5]. Available from: https://www.rch.org.au/clinicalguide/guideline_index/Vitamin_D_deficiency/
61. National Institute for Health Research Centre. Vitamin D: supplement use in specific vitamin D: supplement use in specific population groups population groups Public health guideline. 2014 [cited 2018 Aug 5]. Available from: https://www.nice.org.uk/guidance/ph56/resources/vitamin-d-supplement-use-in-specific-population-groups-pdf-1996421765317

Publisher's Note