INCIDENT KIDNEY DISEASE IN CANADIAN IMMIGRANTS VS. NON-IMMIGRANTS

Ida-Ehosa Olaye[1]

Thesis Primary Supervisor

Manish M Sood[1,3,4] MD MSc FRCPC

Thesis Co-Supervisor

Gregory L. Hundemer [1,2,3,4], MD MPH

Thesis Advisory Committee

Peter Tanusepturo [3,5,6] MD, MSc

Ayub Akbari [4] MD, MSc

Tim Ramsay [1,3], PHD

Greg A. Knoll MD [3], MSc

Affiliations

1 School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

2 ICES, Ottawa, Ontario, Canada

3 Clinical Epidemiology Program, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

4 Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

5 Division of Palliative Care, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

6 Bruyere Research Institute, Ottawa, ON, Canada

8 Division of Nephrology, Department of Medicine, University of Toronto, Toronto, ON, Canada

Thesis submitted to the University of Ottawa in fulfillment of the requirements for the Master of Science in Epidemiology
School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa

PREFACE

Author Contributions

The integral theme and subject matter of this thesis arose from discussions between Ida-Ehosa Olaye, Dr. Gregory Hundemer, Dr. Manish Sood, and Dr. Greg Knoll.

Ida-Ehosa Olaye was engaged in and accountable for every aspect of this thesis, including: drafting the thesis proposal, background literature review, obtaining access to ICES administrative data, creating a dataset creation plan, statistical analyses, creation of tables and figures, drafting of the thesis, final proof-reading and edits, as well as submission.

Ida-Ehosa Olaye is the first author and Dr. Gregory Hundemer is the senior author for both manuscripts within this thesis. Chengchun Yu, Meltem Tuna, Dr. Hundemer, Dr. Sood, Istvan Mucci, and members of the Thesis Advisory Committee (TAC) assisted in data analysis and fine-tuning my studies through email discussions, informal meetings, and official TAC meetings.

Dr. Sood and Dr. Hundemer provided supervision on each aspect of this thesis, including helping to brainstorm the study design, the statistical methodologies that would be utilized, and the cohort characteristics. Members of the TAC also provided invaluable insight on clinical background and additional acumen during the study design.

Acknowledgements

I would like to give a huge and sincere thank you to my MSc thesis co-supervisor, Dr. Gregory Hundemer, for mentorship, unwavering support, and guidance throughout the long journey that was the creation of my thesis. He was very patient with me and very approachable/open to my many questions. He also supported my career goals; writing me letters of recommendation, being a liaison for meaningful connections and more.

Next, I would like to thank my thesis supervisor Dr. Manish Sood. He has also been an integral part of this project really assisting me with study design and meeting the deadlines I outlined for myself.

I want to give another genuine round of thanks to the ICES staff. Meltem Tuna, Shawn Dhaliwal, and especially my analyst, Chengchun Yu; who played an invaluable role in pulling and cleaning my data for me and assisting me through my SAS questions troubleshooting statistically analysis questions that arose with patience.

I want to thank the members of my TAC (Dr. Peter Tanusepturo, Dr. Ayub Akbari, Tim Ramsay, and Greg Knoll) for their support providing me with valuable feedback during my TAC meetings and throughout my thesis.

I want to give thanks to my parents, Osayande Clifford Olaye, and Erikan Olaye. They really helped push me through this thesis supporting me in the ways they could. I am forever grateful for all they have done for me and the lessons they have taught me.

Finally, I want to give all praise and glory onto God, the source of my strength whom makes all things possible.

Funding

Acknowledgement and thanks are due to the following organizations for the funding I received in order to execute and complete my MSc thesis:

1) University of Ottawa Faculty of Medicine for conferring onto me the Special Merit Scholarship for the first three terms of my MSc ($6000 CAD)

ABSTRACT

Chronic kidney disease is a widespread public health concern that is largely affected by social determinants of health. Social determinants of health are non-medical factors that play a role in the health of an individual. An under-explored social determinant of health in relation to kidney disease is immigrant status. A “healthy immigrant effect”, whereby immigrants experience a health advantage compared to non-immigrants, has previously been reported in relation to other health conditions such as heart disease and diabetes but has never been studied in regard to kidney disease. The link between immigrant status and the development of kidney disease remains poorly understood. On one hand, immigrant populations are often negatively affected by social factors such as poverty, food insecurity, and housing instability, all of which have been linked to worse kidney health outcomes. However, on the other hand, a “healthy immigrant effect”, referring to a reduced prevalence of age-related disease among immigrants compared to their non-immigrant counterparts, has previously been demonstrated with other chronic diseases such as cardiovascular disease, diabetes, and dementia. To better understand the association between immigrant status and kidney disease, we herein conducted a population-based cohort study to compare the incidence of early-stage CKD among immigrants versus non-immigrants in Ontario, Canada.

We begin by taking a look at the burden of kidney disease, how it is measured, and how it is viewed in the context of immigrant status. Next we conducted a population-level, observational cohort study of all adult (≥18 years of age) Ontario residents, including foreign-born immigrant Canadian citizens and non-immigrant Canadian citizens by birth, with normal baseline kidney function (outpatient estimated glomerular filtration rate [eGFR] ≥70 mL/min/1.73m2) between April 1, 2007 and September 30, 2020 utilizing provincial health administrative data from ICES. Utilizing this data we had two main objectives:

1) To determine the incidence of early-stage chronic kidney disease, defined by an estimated glomerular filtration rate (eGFR) measurement less than or equal to 60 mL/min/1.73m2, in Canadian Immigrants compared to their non-immigrant counterparts.

2) To examine the association of more severe forms of kidney disease; a 40% reduction in eGFR or kidney failure, in Canadian immigrants vs. non-immigrants.

Within both objective one and two we also examine how refuges status, landing date and world-region of origin influence the association the association between immigrant status and incident CKD.

In study 1 we found that there was about a 20% reduction (adjusted HR 0.80 [95% CI 0.80-0.81]) in incident CKD risk in immigrants vs. non-immigrants after adjusting for confounders. In study 2 we found that there was about a 30% reduction (adjusted HR 0.70 [95% CI 0.69-0.71]) in composite end-stage kidney disease outcome risk in Canadian immigrants vs. non-immigrants. These trends persisted through sensitivity analyses. Additionally, both recent and remote immigrants had reduced CKD risk compared to non-immigrants in study 1 and 2.

Table of Contents

CHAPTER 1: OVERVIEW AND OBJECTIVES

Problem

Chronic Kidney Disease (CKD) is a widespread public health concern, impacting the lives of many (1). Roughly 1 in 10 Canadians are diagnosed with kidney disease and the number of individuals battling end-stage kidney disease (ESKD) has grown by 35% since 2009 (2). On a global scale, it is estimated that nearly 700 million people around the world are living with chronic kidney disease (3). Patients have more favourable health outcomes when the disease is detected in its early stages before progressing to a chronic condition, but early-stage kidney disease is typically asymptomatic and requires laboratory tests for accurate identification (4). Since there is a high rate of morbidity and mortality researchers have taken significant interest in cultivating a growing number of medications to slow down the progression of kidney disease (e.g., angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBS), sodium-glucose co-transporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists, etc.) (5). In addition to being highly prevalent, chronic kidney disease is strongly associated with increased cardiovascular disease and hypertension risk (6).

Most research on CKD focuses on traditional risk factors such as age, hypertension, diabetes, and cardiovascular disease. (7–10). However, traditional risk factors do not predict CKD risk in its entirety. Recently the World Health Organization has deemed the Social Determinants of Health (SDoH) – non-medical factors that influence health outcomes - to be a major public health concern (WHO). In the 3.9 million Canadians living with CKD, SDoH such as, immigrant status, income level and social environment are increasingly recognized as key factors in CKD risk, progression, and onset of comorbidities (11). The link between immigrant status and kidney disease is presently under-researched and not yet well understood. From one perspective, an individual could say that immigrants have a higher propensity for more adverse social determinants of health such as lower income levels, housing instability, food insecurity, etc.,

(12). Refugee immigrants tend to have even worse SDoH's, being more prone to imprisonment, criminalization, rape, and stressful migration which can negatively impact both their physical and mental health (12). However, from another perspective one might advocate for a "Healthy Immigrant Effect" in which immigrants tend to have better overall health and are less prone to chronic conditions than the native citizens of the destination country.

Canada takes great pride in being an immigrant and refugee friendly country which received 471, 771 permanent immigrants and 804,901 non-permanent residents (13). The country strives to be a cultural mosaic, welcoming and encouraging various cultures to co-exist in one setting). Many immigrants enter Canada with similar or even better self-reported health than the general Canadian population. This is often due to the self-selection process of immigration that favors individuals with higher education and high-quality skills that will assist them in filling in demand jobs and bring value to the country (14). Additionally, immigrants may display positive self-selection in which those with better health conditions such as a healthy diet, physically active/fit, does not smoke etc., choose to migrate. A caveat of the "healthy immigrant effect" is that the health of immigrants often declines with their length of stay in the country as immigrants adopt more of the unfavourable lifestyle habits of individuals in the destination country (15).

Purpose and Rationale

The purpose of this thesis is to assess chronic kidney disease in immigrants compared to non-immigrants in Ontario, Canada. Firstly, we will determine the incidence of early CKD (eGFR < 60 ml/min) in Immigrants compared to non-immigrants. Secondly, we will determine the association of immigrant status and more severe forms of kidney disease, CKD progression and kidney failure, relative to non-immigrants. Our findings will help inform prevention, and monitoring strategies among immigrant populations in the Canadian landscape.

Study Objectives

There are two main study objectives:

1) To determine the incidence of early-stage chronic kidney disease, defined by an estimated glomerular filtration rate (eGFR) measurement less than or equal to 60 mL/min/1.73m^2, in Canadian Immigrants compared to their non-immigrant counterparts. We will also examine how refuges status, landing date and world-region of origin influence the association the association between immigrant status and incident CKD.

2) To examine the association of more severe forms of kidney disease; a 40% reduction in eGFR or kidney failure, in Canadian immigrants vs. non-immigrants. We will also examine the role of refugee status, landing date and world region of origin in this association.

Thesis outline

Chapter 2 will provide a background literature review on the intersection of CKD epidemiology and the social determinants of health (SDoH) focusing on immigrant status. *Chapter 3* presents objective 1 – the incidence of an eGFR<60mL/min/1.73m^2 in immigrants to non-immigrants titled "Incident Chronic Kidney Disease Among Canadian Immigrants: A population-based cohort study". Chapter 4 presents objective 2 examining how the exposure "immigrant status" influences an eGFR decline of 40% and kidney failure in a study entitled "Incident eGFR decline and kidney failure among Canadian Immigrants: A population-based cohort study". *Chapter 5* will summarize these findings as well as a discussion of our studies strengths, limitations, and future directions.

CHAPTER 2: BACKGROUND

Measuring Kidney Function and Defining Kidney Disease

Kidney disease is a type of medical dysfunction in which the kidneys are damaged, hindering their ability to filter blood optimally. Kidney Disease: Improving Global Outcomes (KDIGO) defines CKD as kidney damage or glomerular filtration rate (GFR) <60mL/min/1.73m^2 for 3 or more months, irrespective of cause (4). The presence of albuminuria, clinically defined as an albumin-creatinine ratio >30mg/g in two of three urine spot measurements is used as an indicator of kidney damage (4). This results in excess waste and fluid that the kidneys should have removed from the blood to remain in the body which may then cause other health complications such as heart disease and stroke (16). Structural abnormalities (even if GFR is >60mL/min/1.73m^2) may also be used to define CKD such as hematuria/leukocyturia, changes in renal imaging, renal tubular disorders, albuminuria, and a history of kidney transplantation (6). The final and most severe stage of kidney disease is kidney failure, also known as end-stage kidney disease (ESKD; eGFR 15 ml/min or less). ESKD is a medical condition in which an individual's kidneys fail to filter blood efficiently enough for them to be able to survive without a kidney transplant or dialysis (16).

The current body of literature based on a series of clinical trials, meta-analyses of cohorts, and simulations of trial designs and analytical methods suggests that an eGFR decline of 30% over 2 to 3 years may be an acceptable biomarker for severe kidney disease (17). However, the National Kidney Foundation and Food and Drug Administration concluded that a 40% reduction in eGFR, corresponding to a 1.5-fold increase in serum creatinine level, represents an even more widely applicable approach to representing severe kidney disease (18).

Burden of Kidney Disease

CKD is an increasingly recognized chronic illness, affecting approximately 4 million Canadians (19) with roughly 50,000 Canadians combating end-stage kidney disease (42% are receiving a functional kidney transplant and 58% are on dialysis for treatment (2,19). In the United States

the Centers for Disease Control (CDC) estimates that 15% of Americans have CKD (20). On a global scale, nearly 700 million people around the world (8.9%) have CKD, it is a disease impacting the lives of many (3). CKD is especially common in diabetics and is a large contributor to disability-adjusted life-years (DALY) (3). In 2017 diabetic nephropathy accounted for nearly a third of DALYs (3). Additionally, CKD is associated with an increased risk of cardiovascular disease, hypertension, death, and morbidity (6). Data from 2013 revealed that CKD was associated with 4% of deaths worldwide (2.2 million deaths) (6). Of these deaths, 0.96 million were related to kidney failure while cardiovascular diseases were the cause of more than half of these deaths (21).

Immigrant Status and Kidney Disease

Canada has one of the highest immigration rates in the world. Nearly a quarter of individuals residing in Canada are immigrants and about 45% of immigrants to Canada settle down in Ontario each year (13,22). Many present-day Canadian immigrants are racialized and often face implicit or overt bias and micro-and-macro aggressions even in the health-sector which could impact their health outcomes often leading to greater risk of CKD progression relative to white counterparts (23–25). In a study examining the prevalence of ESKD in Ontario immigrants vs. long-term residents, the immigrants with ESKD were found to be younger, and have a larger proportion in the lowest income quintile than their long-term resident counterparts(26). Refugee immigrants – those who have been forced to flee their home country due to violence, war, or persecution, along with those residing in Canada without legal immigrant status such as those on temporary work permits and student visa's often face elevated stress levels, housing instability, and reduced social support adversely affecting their physical and mental health (27). However, in Canada healthcare is government funded providing healthcare access to all residents. All 10 provinces in Canada have universal healthcare insurance plans which cover physician care and hospitalization (28). The federal government covers 20-30% of the total healthcare cost while the provinces are responsible for contributing the remaining balance,

ensuring adequate delivery of care, and administering funds (29).

One may automatically predict Canadian immigrants to have worse health outcomes than non-immigrants, however, the “healthy immigrant effect” suggests the contrary. As aforementioned the “healthy immigrant effect” is a phenomenon in which immigrants tend to have better overall health and reduced prevalence of chronic diseases compared to their native-born counterparts in the destination country. With increasing duration of stay the health of immigrants begins to mirror that of natives as they adopt the lifestyle behaviors of the native population. For example, in a study using 2014 Canadian Community Health Survey (CCHS) data, researchers Adeji et al., found recent immigrants to be less likely to have type II diabetes than the native-born Canadian population (OR=0.46, CI=0.27-0.79) (30). In a population-based retrospective cohort study using 1985-2005 linked immigration and health data from Ontario, Canada, researchers found that immigrants had a lower adjusted risk of cardiovascular events or mortality (adjusted hazard ratio [HR] 0.76, 95% CI 0.74-0.78) compared to long-term residents (31).

Both diabetes and cardiovascular disease are risk factors for CKD (31). The majority of studies examining the influence of immigrant status on CKD assess prevalence as opposed to incidence and have conflicting findings. Some stating that CKD generally higher in immigrants than non-immigrants and some concluding the reverse findings CKD prevalence to be lower in immigrants than natives (26,32).

Summary of Prior Relevant Studies:

Study	**Major Findings**	**Limitations**
ESRD among Immigrants to Ontario, Canada: A Population-Based Study. Perl et al. 2018	The point prevalence values for ESRD-D among immigrants and long-term Canadian residents were 89.4 per 100,000 and 100.5 per 100,000, respectively. After adjusting for age, the prevalence of ESRD-D was higher among immigrants compared with long-term Canadian residents (age-adjusted PR, 1.29' 95% CI, 1.23 to 1.26; long-term Canadian residents are the referent group) (26)	Researchers were unable to distinguish between Canadian born individuals and long-term residents who immigrated to Canada before 1985. Such misclassification may have attenuated the magnitude of the relative relationship between immigrant status and the risk of ESRD-D. Researchers also had no information on the ethnicity of long-term residents, some of whom themselves might have been immigrants.
The Relationship Between Immigration Status and Chronic Kidney Disease Risk Factors in Immigrants and US-Born Adults. Dawson et al. 2020	Immigrants were significantly less likely to have an eGFR < 60 (OR 0.42, 95% CI 0.36–0.50), which remained after adjustment (OR 0.75, 95% CI 0.61–0.93). Immigrants had significantly lower odds of having an eGFR < 60 compared to US-born adults. Additionally, immigrants with ≥ 15 years in the US had mean eGFR values that were less than immigrants < 15 years in the US, indicating that there is some decrease in kidney function as the length of US residence increases.(32)	Urinary albumin and urinary creatinine were measured in a random urine collected in the mobile examination center (MEC). Creatinine from this collection was used to calculate eGFR using CKD-EPI equation. Researchers were unable to make a diagnosis of CKD in study population since a decrease in eGFR (< 60 ml/min/1.73m2) or evidence of kidney damage lasting three or more months is required. (32)

Social determinants of health and the transition from advanced chronic kidney disease to kidney failure. Hundemer 2023	Not having a high school degree was associated with higher odds for an inpatient dialysis start compared with having a college degree {odds ratio [OR] 1.71 [95% confidence interval (CI) 1.09–2.69]}. Unemployment was associated with higher odds for an inpatient dialysis start [OR 1.85 (95% CI 1.18–2.92)], lower odds for pre-emptive access creation [OR 0.53 (95% CI 0.34–0.82)] and lower odds for pre-emptive kidney transplantation [OR 0.48 (95% CI 0.24–0.96)] compared with active employment. Being single was associated with higher odds for an inpatient dialysis start [OR 1.44 (95% CI 1.07–1.93)] and lower odds for pre-emptive access creation [OR 0.67 (95% CI 0.50–0.89)] compared with being married.(33)	The number of patients receiving pre-emptive kidney transplants was relatively low which limited the statistical power of the study. It was a single-center study which negatively impacts generalizability. Income level, literacy, housing status, neighborhood environment, and race were not captured as social determinants. (33)
Disparities in chronic kidney disease-the state of the evidence. Clark-Cutaia et al. 2021	The literature, although conflicting at times, indicates racial and ethnic minorities with predialysis CKD experience disparities of progression and mortality; however, once on dialysis, appear to live longer than their white counterparts. There are strikingly few studies about US immigrants with CKD despite the fact that many immigrant groups are	Little knowledge exists regarding the root of the disparities and how to best address them. More research needs to utilize prospective research methods in North American CKD cohorts. (23)

	at high risk for CKD due to a variety of factors(23).	
The Healthy Immigrant Effect and Aging in the United States and Other Western Countries. Markides 2019	A growing literature on immigrant health and aging has consistently found that voluntary "economic" immigrants to the United States, Australia, and Canada, and to a lesser extent to Europe, appear to be healthier than native populations. Researchers have proposed several explanations for this health advantage, including healthy immigrant selection, health-promoting behaviors, and sociocultural resources. From the extant literature, immigrant health selection appears to the main explanation for the immigrant health advantage, which is typically more clearly observed in mortality than in other measures of health. (34)	There has been a recent surge of immigrants from Asia, especially China and India, to the United States, Canada, and Australia. These changes to the immigrant population will require greater attention to their health status and uncovering whether the same processes account for a mortality advantage and age-related convergence with these growing immigrant groups. As has been established in Europe and elsewhere refugees are much less heath selected than other immigrants and experience more psychological and physical problems, especially those arriving in the older years. Needless to say, very little is known regarding refugees in the Middle East, Africa, and elsewhere
The association between local area immigrant fraction and prevalence of cardiovascular diseases in the United States: an observational study. Shokeen et al. 2023	The central finding of this study is that increasing the local area immigrant fraction is associated with decreasing local prevalence of CHD, and to a lesser extent stroke in the United States. These findings remained consistent when analyzing the two largest immigrant subgroups, Asians and Hispanics. In CHD, there exists a direct contribution of immigrant fraction on disease prevalence, which accounts	The independent and dependent variables were not measured at the level of the individual, but rather at the level of Zip Code Tabulated Area (ZCTA). Researchers therefore could not decompose CHD or stroke prevalence between immigrants and non-immigrants (or between racial groups) within a ZCTA. Researchers also could not decompose health behavioral patterns or demographic

	for 45% of the total association There also exist significant indirect associations with immigrant fraction and CHD (~55%) mediated through lower prevalence of deleterious health behaviors (smoking, physical activity, annual health checkups, cholesterol screening, having health insurance). The association with immigrant fraction and stroke was evident as well but largely mediated through health behaviours (7)	profiles within a ZCTA by group. Shokeen et al., chose to exclude low-immigrant communities in the main analyses. These excluded ZCTAs (~16,000) were found predominantly in rural communities throughout the US. As such, the generalizability of our findings to less populated and more rural regions of the US may be limited. (7)
Association of Birthplace and Coronary Heart Disease and Stroke Among US Adults: National Health Interview Survey, 2006 to 2014.	Age-standardized prevalence of both CHD and stroke were higher among US- than foreign-born adults (CHD: 8.2% versus 5.5% for men and 4.8% versus 4.1% for women; stroke: 2.7% versus 2.1% for men and 2.7% versus 1.9% for women; all $P<0.05$). (8)	The NHIS was conducted among noninstitutionalized US residents, and therefore, those in long-term care facilities were not included in the survey. It is possible that adults with CHD and/or stroke were more likely to be in these facilities than those without CHD and/or stroke, especially immediately after a cardiovascular disease event. It is also possible that foreign-born adults, who were less likely to have health insurance coverage, will be less likely to be in long-term care facilities. The health data was collected through self-report surveys which are subject to recall bias. (8)
Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. Vang et al. 2017	The healthy immigrant effect (HIE) appears to be strongest during adulthood but less so during childhood/adolescence and late life. A foreign-born health advantage is also more robust for mortality but less so for morbidity. The HIE is	The same databases were used multiple times across many of the studies. Consequently, this synthesis is based on a smaller number of effective studies. Likewise, within each life-course stage, studies that contained multiple health indicators

	also stronger for more recent immigrants but further research is needed to determine the critical threshold for when migrants' advantage disappears. Positive selection as an explanation for the HIE remains underdeveloped.(14)	were coded more than once. This means that there may be greater emphasis on some results than is warranted. There were very few studies of immigrant health during childhood and late life. Thus, our review of the HIE during these two life-course stages are preliminary and will require additional studies for more definitive assessments of migrant children's and seniors' health advantage or lack thereof. (14)

Importance of Early Detection

It is advantageous to detect CKD in its early stages because the sooner one can receive treatment interventions such as medications to slow disease progression (e.g., ACE inhibitors, ARBS, SGLT2 inhibitors, etc.), the lower their risk of progression to kidney failure as well as a reduced risk of cardiovascular events (35). Early detection of CKD is also very important because the beginning stages of the disease are often asymptomatic, and patients typically do not notice obvious signs of kidney damage until the disease is more advanced (35). Detection of early CKD (eGFR < 60 ml/min) would aid in disease progression and mitigation of CKD-related complications

CHAPTER 3: MANUSCRIPT I: INCIDENT CHRONIC KIDNEY DISEASE AMONG CANADIAN IMMIGRANTS: A POPULATION-BASED COHORT STUDY

Ida-Ehosa Olaye BSc[1,2], Manish M. Sood MD MSc[3,4], Chengchun Yu PhD[2], Meltem Tuna PhD[2,4], Ayub Akbari MD MSc[3,4], Peter Tanuseputro MD MSc[5,6], Istvan Mucsi MD PhD[7,8], Greg A. Knoll MD MSc[3,4], and Gregory L. Hundemer MD MPH[3,4]

Affiliations:

[1] School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

[2] ICES, Ottawa, Ontario, Canada

[3] Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[4] Clinical Epidemiology Program, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

[5] Division of Palliative Care, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[6] Bruyere Research Institute, Ottawa, ON, Canada

[7] Ajmera Transplant Centre and Division of Nephrology, University Health Network, Toronto, ON, Canada

[8] Division of Nephrology, Department of Medicine, University of Toronto, Toronto, ON, Canada

Correspondence To:

Dr. Gregory L. Hundemer

Ottawa Hospital – Riverside Campus

1967 Riverside Drive, Office 5-33

Ottawa, ON, Canada K1H 7W9

Phone: (613) 738-8400; Fax: (613) 738-8337
Email: ghundemer@toh.ca

Word Count:

Abstract: 297

Manuscript Body: 3,050

References: 46

Figures: 3

Tables: 2

ABSTRACT

Introduction: A “healthy immigrant effect” has been demonstrated for a number of chronic health conditions including cardiovascular disease, diabetes mellitus, and dementia; however, the link between immigrant status and kidney health remains uncertain. We sought to compare the risk for incident chronic kidney disease (CKD) between Canadian immigrants and non-immigrants.

Methods: We conducted a population-level, observational cohort study of all adult (≥18 years of age) Ontario residents, including foreign-born immigrant Canadian citizens and non-immigrant Canadian citizens by birth, with normal baseline kidney function (outpatient estimated glomerular filtration rate [eGFR] ≥70 mL/min/1.73m^2) between April 1, 2007 and September 30, 2020 utilizing provincial health administrative data. Multivariable Cox proportional hazard regression modeling was used to evaluate the relationship between immigrant status and the development of incident CKD (outpatient eGFR <60 mL/min/1.73m^2).

Results: The study cohort included 10,440,210 Ontario residents, consisting of 22% immigrants (N = 2,253,360) and 78% (N = 8,186,850) non-immigrants. The mean (SD) age and eGFR were 45 (17) years and 102 (16) mL/min/1.73m^2, respectively, and 54% of individuals were female. A total of 117,028 immigrants (5%, 7 events per 1,000 person-years) and 984,277 non-immigrants (12%, 16 events per 1,000 person-years) developed incident CKD during follow-up. Immigrants experienced a 20% lower risk for incident CKD compared to non-immigrants (adjusted hazard ratio 0.80 [95% confidence interval 0.80-0.81]). Consistent findings were seen for refugee and non-refugee immigrants, immigrants with remote (1985-2004) and recent (2005-2020) landing dates, and immigrants from different world regions. Results were similar upon re-defining incident CKD as two outpatient eGFR measurements <60 mL/min/1.73m^2 at least 90 days apart, treating death as a competing risk, and adjusting for baseline albuminuria.

Conclusion: Immigrants experience a lower risk for incident CKD compared to non-immigrants. These findings provide evidence of a "healthy immigrant effect" in relation to kidney health.

KEY QUESTIONS

What is already known on this topic?

- Chronic kidney disease (CKD) is a major global health issue, affecting over 800 million people worldwide.
- Immigrant populations are often negatively affected by social factors such as poverty, food insecurity, and housing instability, all of which have been linked to worse kidney health outcomes
- A "healthy immigrant effect" has been demonstrated for a number of chronic health conditions including cardiovascular disease, diabetes mellitus, and dementia;

however, the link between immigrant status and kidney health remains uncertain.

What this study adds?

- In this population-based observational cohort study, immigrants to Canada experienced a 20% lower risk for incident CKD compared to Canadian-born adults.
- Apart from immigrants from North America, immigrants from all other world regions experienced a lower risk for incident CKD compared to Canadian-born adults.
- As with other chronic health conditions, a "healthy immigrant effect" exists in relation to kidney health.

How this study might affect research, practice or policy?

- Future studies are necessary to determine why immigrants experience lower rates of CKD and to compare the longitudinal trends in CKD progression between immigrants and non-immigrants.
- An enhanced understanding of how longitudinal health trends vary among immigrants based on factors such as refugee status and country of origin may inform health policy decisions surrounding immigrant health screening and resource allocation.

INTRODUCTION

Chronic kidney disease (CKD) is a major global health issue, affecting over 800 million people worldwide.[1] In Canada, it is estimated that CKD affects one in ten individuals.[2] CKD is defined either by evidence of kidney damage, indicated by albuminuria, or more commonly by a reduction in kidney function, indicated by a reduction in glomerular filtration rate (GFR). The standard estimated GFR (eGFR) cutoff adopted to define CKD is <60 mL/min/1.73m^2 as this

represents a decline in kidney function to approximately half of what is seen in healthy young adults and associates with increased morbidity and mortality at the population level.[3 4] CKD predisposes to a host of health complications including hypertension, cardiovascular disease, anemia, kidney failure, death, and reduced quality of life.[5] Therefore, early detection and treatment of CKD is imperative to slow its progression and prevent adverse CKD-related outcomes.

Social determinants of health (i.e., non-medical factors that influence health outcomes) are increasingly recognized to be strongly linked to both CKD incidence and outcomes. For instance, factors such as race/ethnicity, unemployment, poverty, and low education are associated with poor kidney health.[7-18] An understudied social determinant of health in relation to kidney disease is immigrant status. Canada takes great pride in being an "immigrant friendly" country, becoming a major destination for immigrants globally. Universal health care coverage begins shortly after an immigrant arrives in Canada. Current immigration rates in Canada are among the highest for any country in the world and continue to rise, translating into approximately one quarter of the Canadian population being comprised of foreign-born immigrants.[1]

The link between immigrant status and the development of kidney disease remains poorly understood. On one hand, immigrant populations are often negatively affected by social factors such as poverty, food insecurity, and housing instability, all of which have been linked to worse kidney health outcomes.[20] On the other hand, a "healthy immigrant effect", referring to a reduced prevalence of age-related disease among immigrants compared to their non-immigrant counterparts, has previously been demonstrated with other chronic diseases such as cardiovascular disease, diabetes, and dementia.[21-25] To better understand the association between immigrant status and kidney disease, we herein conducted a population-based cohort study to compare the incidence of early-stage CKD among immigrants versus non-immigrants in Ontario, Canada.

METHODS

Study Design and Setting

We conducted a population-level, observational cohort study of adults ≥18 years of age in Ontario, Canada with normal baseline kidney function (outpatient eGFR ≥70mL/min/1.73m^2) using linked databases held at ICES (formerly, Institute for Clinical Evaluative Sciences). Ontario is Canada's largest province with over 15 million residents.[26] ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. The reporting of this study follows guidelines for observational studies (**Supplemental Table 1**).[27]

Data Sources

We ascertained baseline characteristics and outcome data from de-identified, linked databases housed at ICES. Demographic and vital status information was obtained from the Ontario Registered Persons Database. Immigrant-specific information was obtained from the Immigrant Refugees and Citizenship Canada (IRCC) database[28]. Diagnostic and procedural information from all hospitalizations were determined using the Canadian Institute for Health Information Discharge Abstract Database. Diagnostic information from emergency room and day surgery visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan (OHIP) database, which contains all health claims for inpatient and outpatient physician services. Laboratory information is contained in the Ontario Laboratory Information System (OLIS) which captures laboratory tests for all patients in Ontario. Definitions for patient characteristics and clinical variables can be found in **Supplemental Table 2**. These datasets were linked using unique encoded identifiers and

analyzed at ICES. The databases were complete for all variables used except for rural residence, neighborhood income quintile, and immigrant world region of origin, which were missing in <0.5% of individuals. The only reason for lost follow-up was emigration from the province which occurs in <0.5% of Ontario residents annually.[29]

Cohort Definition

We included all Ontario residents ≥18 years of age that had an index outpatient eGFR measurement ≥70mL/min/1.73m^2 between April 1, 2007 and September 30, 2020. The date of this initial eGFR measurement served as the study index date, date of cohort entry, and beginning of follow-up. Individuals with an outpatient eGFR <70 mL/min/1.73m^2 at index, a history of dialysis, or prior kidney transplantation were excluded. eGFR was calculated using the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based equation.[30] Individuals were followed from index date until the outcome of interest or censoring (emigration from Ontario, death, or end of study period).

Exposure

The primary exposure was immigrant status, specifically whether an individual was a foreign-born immigrant Canadian citizen or a non-immigrant Canadian citizen by birth. All immigrants to Canada since 1985 are captured in the IRCC database upon arrival.

Outcomes

The primary outcome was incident CKD, defined as an outpatient eGFR <60 mL/min/1.73m^2. Inpatient or emergency room eGFR measurements were not included so as to minimize the risk of capturing acute kidney injury (AKI) events. A single outpatient eGFR measurement has previously been shown to provide an accurate estimate of kidney function in a similar ICES-based cohort[31] and external cohorts.[32 33] We further assessed the outcome of incident CKD in alignment with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as two

outpatient eGFR measurements <60 mL/min/1.73m^2 at least 90 days apart.[34]

Statistical Analysis

Baseline characteristics were ascertained for immigrants and non-immigrants. Continuous variables were reported as mean (standard deviation [SD]) while categorical variables were reported as number (%). Crude CKD incidence rates (events/1,000 person-years) were calculated for immigrants and non-immigrants. Multivariable Cox proportional hazards modeling was used to measure the association between immigrant status and incident CKD. Models were adjusted for the following variables selected *a priori* based upon clinical knowledge and previous literature: age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery).[5] Additional multivariable Cox models were used to compare the risk for incident CKD between: A) refugee versus non-refugee immigrants, B) immigrants with remote [1985-2004] versus recent [2005-2020] landing dates, and C) immigrants coming to Canada from different regions of the world. We conducted all analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). 95% confidence intervals (CI) that did not overlap with 1.0 and two-sided p-values <0.05 were treated as statistically significant.

Additional Analyses

Additional analyses included: A) re-defining the incident CKD outcome as two outpatient eGFR measurements <60 mL/min/1.73m^2 at least 90 days apart as per KDIGO guidelines,[34] B) utilizing Fine-Gray sub distribution hazard models accounting for the competing risk of death, and C) restricting the study cohort to those with a urine albumin-to-creatinine ratio [UACR] within one year of index and adjusting for UACR within the regression models.

RESULTS

Baseline Characteristics

From a total of 12,007,777 Ontario residents with an eGFR measurement within the accrual period, 10,440,210 met our inclusion criteria (**Figure 1**). The study cohort consisted of 2,253,360 (22%) immigrants and 8,186,850 (78%) non-immigrants (**Table 1**). The mean (SD) age of the cohort was 45 (17) years with immigrants being slightly younger. Females made up 54% of the cohort which was similar among both immigrants and non-immigrants. The mean (SD) baseline eGFR of the cohort was 102 mL/min/1.73m^2 with immigrants having slightly higher values. Immigrants generally lived in neighborhoods with lower income levels, less commonly resided in rural areas, and had fewer comorbidities. Immigrant-specific characteristics are displayed in **Table 2**. Refugees represented 17% of the immigrant population. Immigrants came from all regions around the world with approximately half coming from Asia.

Incident Chronic Kidney Disease by Immigrant Status

A total of 117,028 immigrants (5%) and 984,277 non-immigrants (12%) developed incident CKD over the follow-up period. This translated into a crude incidence rate 7 events/1,000 person-years for immigrants as compared to 16 events/1,000 person-years for non-immigrants. In the multivariable Cox regression models, immigrants experienced a 20% lower risk for incident CKD compared to non-immigrants (adjusted hazard ratio [aHR] 0.80 [95% CI 0.80-0.81]) – the adjusted cumulative incidence curves are displayed in **Figure 2**. Both refugee (aHR 0.87 [95% CI 0.86-0.89]) and non-refugee immigrants (aHR 0.79 [95% CI 0.79-0.80]) experienced a lower risk for incident CKD compared to non-immigrants. Immigrants with remote (1985-2004; aHR 0.78 [95% CI 0.78-0.79]) and recent (2005-2020; aHR 0.87 [95% CI 0.86-0.88]) landing dates experienced a lower risk for incident CKD compared to non-immigrants.

Incident Chronic Kidney Disease among Immigrants by World Region

Figure 3 displays the risk of incident CKD for immigrants by world region. There was no difference in incident CKD risk between immigrants from North America compared to non-immigrants (aHR 0.99 [95% CI 0.97-1.01]). There was a progressively lower risk for incident CKD among immigrants from Africa (aHR 0.97 [95% CI 0.95-0.99]), South America (aHR 0.90 [95% CI 0.88-0.93]), Middle East (aHR 0.89 [95% CI 0.87-0.91]), Europe (aHR 0.78 [95% CI 0.77-0.80]), and Asia (aHR 0.73 [95% CI 0.72-0.74]) compared to non-immigrants.

Additional Analyses

Results were similar upon re-defining incident CKD as two outpatient eGFR measurements <60 mL/min/1.73m^2 at least 90 days apart (**Supplemental Table 3**), treating death as a competing risk (**Supplemental Table 4**), and adjusting for baseline UACR in the subset of individuals with UACR measurements within one year of index (n=5,831 immigrants, n=25,461 non-immigrants) (**Supplemental Table 5**).

DISCUSSION

In this large population-based cohort study of Ontario residents, we found that immigrants experienced a 20% lower risk for incident CKD compared to non-immigrants. The lower risk for incident CKD was present in refugee and non-refugee immigrants, immigrants with remote versus recent landing dates, and immigrants from different world regions. These findings were consistent after adjusting for known potential confounding factors and across multiple sensitivity analyses.

The seemingly protective effect of being an immigrant on CKD incidence may be explained by the “healthy immigrant effect”. This term refers to a phenomenon whereby immigrants have a health advantage over their domestic-born counterparts.[21-25] For example, a systematic review found that adult immigrants had similar or better health compared to Canadian-born adults, particularly in regard to chronic health conditions.[35] This may relate to differences in health-related behaviors among immigrants such as healthier diet, increased physical activity, lower

alcohol consumption, and reduced smoking rates.[23 24 36-38] The “healthy immigrant effect” may also be explained by the immigration selection process itself with healthier individuals being more likely to immigrate and less healthy individuals being more likely to remain in their country of origin.[39 40] Specific to the Canadian immigration process, a point system is employed based upon human capital which favors individuals with higher education and language skills for the economic class of immigrants that will contribute to successful living post-migration.[35 41] Notably, these social factors are known to correlate with better health, including kidney health.[15 16 18] Further, the medical screening tests required during the immigration process may promote systematic selection. While this “healthy immigrant effect” has been shown to diminish over time in relation to other chronic health conditions, due to stressors in adjusting to a new living environment and adoption of unhealthy behaviors,[38 42 43] we found a sustained effect in relation to CKD incidence even among immigrants with remote landing dates.

While the “healthy immigrant effect” is well-established for chronic health conditions such as cardiovascular disease, diabetes, and dementia,[21-25] its linkage with kidney health is less well understood. The present study demonstrates that the “healthy immigrant effect” does indeed extend to kidney disease as well with a lower incidence of early-stage CKD. These findings are consistent with a previous study from the United States using National Health and Nutrition Examination Survey (NHANES) data which showed that prevalent CKD (rather than incident CKD as with the present study) was less common among immigrants.[44] In contrast, an Ontario-based study found that the prevalence of end-stage kidney disease (ESKD) requiring dialysis was higher among immigrants compared to long-term Canadian residents.[45] Perhaps these conflicting findings in relation to early-stage CKD and ESKD reflect the inherent challenges with comparing studies of incident rather than prevalent kidney disease.

An interesting finding relates to the differential incident CKD risk based on world region. There was no difference in incident CKD risk for immigrants from North America, individuals who may be most similar to Canadian-born adults in regard to not only geography but also health-related

behaviors. Immigrants from all other regions experienced a lower incident CKD risk. However, the absolute effect size was minimal for immigrants from Africa which may relate to predisposing CKD risk factors common among individuals of African descent such as APOL1 variants.[46]

Future studies are necessary to improve our understanding for why immigrants experience lower rates of early-stage CKD. Studies on CKD progression and the development of CKD risk factors may provide insight and potential early therapeutic intervention targets. A better understanding of the longitudinal trends in disease states known to predispose to CKD (e.g., hypertension and diabetes) will further serve to identify individuals who will benefit from ever-improving pharmacologic treatment options. Additionally, understanding how these longitudinal health trends vary among immigrants based on factors such as refugee status and country of origin may allow for enhanced screening approaches and resource allocation.

Our results must be interpreted within the context of the study design. First, this study was observational; therefore, we were able to identify association but not causation. However, our analytic models adjusted for numerous potential confounders that should reduce observed confounding though we acknowledge that unobserved confounding may still occur. Second, our primary analysis defined incident CKD as a single outpatient eGFR measurement <60 mL/min/1.73m^2 which may lead to some degree of misclassification (e.g., outpatient AKI). However, our results were consistent upon re-defining incident CKD as two outpatient eGFR measures <60 mL/min/1.73m^2 at least 90 days apart, consistent with KDIGO guidelines.[34] Third, CKD is defined not only by a reduction in kidney function (eGFR) but also by kidney damage (albuminuria). The results from a sensitivity analysis adjusting for UACR among the subset of individuals with available measures within one year of index were consistent. Fourth, medication data in Ontario is available only for individuals ≥65 years of age. As the vast majority of our cohort was below this age cutoff, we were unable to adjust for medications that may impact kidney function (e.g., renin-angiotensin-aldosterone system inhibitors, sodium-glucose

cotransporter-2 inhibitors, etc.). Finally, as the IRCC database captures all immigrants to Canada from 1985 onwards, we were unable to distinguish between individuals who were born in Canada and long-term residents who immigrated to Canada prior to 1985. This misclassification may have attenuated the magnitude of the associations between immigrant status and incident CKD risk.

CONCLUSION

In this population-based observational cohort study, immigrants to Canada experienced a 20% lower risk for incident CKD compared to Canadian-born adults. The lower CKD risk was observed among both refugee and non-refugee immigrants and among both immigrants with remote (1985-2004) and recent (2005-2020) landing dates. Apart from immigrants from North America, immigrants from all other world regions experienced a lower risk for incident CKD compared to Canadian-born adults. These findings provide evidence of a "healthy immigrant effect" in relation to kidney health. Future studies are necessary to determine why immigrants experience lower rates of CKD and to compare the longitudinal trends in CKD progression between immigrants and non-immigrants. An enhanced understanding of how longitudinal health trends vary among immigrants based on factors such as refugee status and country of origin may inform health policy decisions surrounding immigrant health screening and resource allocation.

ACKNOWLEDGEMENTS

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This document used data adapted from the Statistics Canada Postal Code^{OM} Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information

compiled and provided by: the Canadian Institute for Health Information and Ontario MOH. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Additionally, parts or whole of this material are based on data and/or information provided by Immigration, Refugees and Citizenship Canada (IRCC) current to September 2020. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of IRCC.

CONTRIBUTORS

IO, MMS, PT, GLH conceptualized the study. IO, CY, MT conducted data management and statistical analysis. MMS, AA, PT, IM, GAK, GLH provided overall supervision of the manuscript. IO and GLH drafted the first manuscript. All authors provided critical revision and editing of the manuscript. All authors read and approved the final manuscript.

FUNDING

GLH is supported by the Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes (Reference # PJT-183840) and the Lorna Jocelyn Wood Chair for Kidney Research.

COMPETING INTERESTS

MMS reports receiving speaker fees from AstraZeneca, Otsuka, Bayer, and GlaxoSmithKline, all outside of the submitted work. AA reports receiving speaker fees from AstraZeneca and holds research grants from Otsuka, all outside of the submitted work. No other competing interests declared.

PATIENT AND PUBLIC INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or

dissemination plans of this research.

DATA AVAILABILITY STATEMENT

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

CHAPTER 4: eGFR DECLINE AND KIDNEY FAILURE AMONG IMMIGRANTS: A POPULATION-BASED COHORT STUDY

Ida-Ehosa Olaye BSc[1,2], Chengchun Yu PhD[2], Meltem Tuna PhD[2,3], Ayub Akbari MD MSc[3,4], Tim Ramsay PhD[1,3], Peter Tanuseputro MD MSc[5,6], Istvan Mucsi MD PhD[7,8], Greg A. Knoll MD MSc[3,4], Manish M. Sood MD MSc[3,4*], and Gregory L. Hundemer MD MPH[2,3,4*]

[*] Contributed equally as co-senior authors.

Affiliations:

[1] School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

[2] ICES, Ottawa, Ontario, Canada

[3] Clinical Epidemiology Program, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

[4] Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[5] Division of Palliative Care, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[6] Bruyere Research Institute, Ottawa, ON, Canada

[7] Ajmera Transplant Centre and Division of Nephrology, University Health Network, Toronto, ON, Canada

[8] Division of Nephrology, Department of Medicine, University of Toronto, Toronto, ON, Canada

Running Headline: Longitudinal Kidney Health among Immigrants

Correspondence To:

Dr. Gregory L. Hundemer

Ottawa Hospital – Riverside Campus

1967 Riverside Drive, Office 5-33

Ottawa, ON, Canada K1H 7W9

Phone: (613) 738-8400; Fax: (613) 738-8337; E-mail: ghundemer@toh.ca

Sources of Support:

1. Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes - Reference # PJT-183840 (GLH)

2. Lorna Jocelyn Wood Chair for Kidney Research (GLH)

Word Count:

Abstract: 244

Lay Summary: 148

Main Text: 3,517

References: 49

Tables: 3

Figures: 3

ABSTRACT

The link between immigrant status, a key social determinant of health, and kidney health remains uncertain. Herein, we sought to compare the risk for incident adverse kidney outcomes between immigrants and non-immigrants. Using Canadian provincial health administrative data, we conducted a population-based observational cohort study of all adult Ontario residents (immigrants and non-immigrants) with normal baseline kidney function (eGFR ≥70 mL/min/1.73m^2). Multivariable Cox proportional hazard regression modeling was used to evaluate the relationship between immigrant status and a composite adverse kidney outcome of 40% eGFR decline or kidney failure. The study cohort included 10,440,210 individuals with 22% immigrants and 78% non-immigrants. The mean (SD) age and eGFR were 45 (17) years and 102 (16) mL/min/1.73m^2, respectively. Immigrants experienced a 30% lower risk for the composite adverse kidney outcome (adjusted hazard ratio [aHR] 0.70 [95% CI 0.69-0.71]) compared to non-immigrants which was primarily driven by 40% eGFR decline. However, immigrants also experienced a 21% lower risk for incident kidney failure (aHR 0.79 [95% CI 0.75-0.83]) compared to non-immigrants. Results were consistent upon accounting for the competing risk of death and adjusting for baseline albuminuria. As has been demonstrated with other chronic diseases, these novel findings suggest that a healthy immigrant effect also exists in regard to kidney disease. Differential kidney disease risks were identified among immigrants based on landing date, refugee status, and world region of origin which may inform health policy decision-making toward targeted screening strategies and more cost-effective resource allocation for immigrant populations.

KEYWORDS

Immigrant

Refugee

Social determinants of health

Kidney health

Chronic kidney disease (CKD)

End-stage kidney disease (ESKD)

LAY SUMMARY

Social determinants of health are non-medical factors that play a role in an individual's health, including kidney health. An under-explored social determinant of health in relation to kidney disease is immigrant status. A "healthy immigrant effect", whereby immigrants experience a health advantage compared to non-immigrants, has previously been reported in relation to other health conditions such as heart disease and diabetes but has never been studied in regard to kidney disease. This study across a broad Canadian population now shows that a "healthy immigrant effect" also applies to kidney disease as immigrants were less likely to experience a decline in kidney function or require dialysis. However, kidney disease risk among immigrants varied based on factors such as if they were a refugee and what country they migrated from. A better understanding of these differences among immigrants may help to provide more targeted care to specific high-risk immigrant populations.

INTRODUCTION

Social determinants of health are increasingly recognized to play a role in kidney health. The term "social determinants of health" refers to non-medical factors that exert a major influence on health outcomes.[1] This includes factors such as education, employment, income, literacy, race/ethnicity, and home environment. Numerous studies have demonstrated that such social factors are strongly linked to kidney outcomes including chronic kidney disease (CKD), kidney failure, dialysis access creation, "crash" dialysis starts, and kidney transplantation.[2-16] In modern day practice, information about social determinants of health is not typically incorporated into routine nephrology practice. Increasing the awareness of how social determinants of health may impact kidney disease has been emphasized as a target area for improvement within the

nephrology community.[17, 18]

An underexplored social determinant of health in regard to kidney disease is immigrant status. Specifically, it remains unknown whether immigrants experience a differential risk (increased or decreased) for kidney disease compared to non-immigrants. Immigrants have a higher propensity for deleterious social determinants of health including poverty, unemployment, unstable housing, food insecurity, and racial disparities which predispose to adverse kidney health outcomes.[19, 20] Conversely, a healthy immigrant effect has previously been described for a number of chronic diseases including cardiovascular disease and diabetes mellitus.[21-26] The term “healthy immigrant effect” refers to a phenomenon whereby immigrants experience a health advantage compared to their domestic-born counterparts which has been hypothesized to relate to healthier lifestyle behaviors.[23, 24, 27-29] The limited existing literature on immigrant status and kidney health has focused on prevalent, rather than incident, kidney disease and has yielded conflicting results.[30, 31]

Canada is an ideal location in which to evaluate the link between immigrant status and kidney health as it is an “immigrant friendly” nation with an immigration rate among the highest in the world. In fact, 20 to 25% of the Canadian population is made up of foreign-born immigrants. Moreover, universal health care coverage begins shortly after immigration to Canada, thus minimizing access to health care as a barrier relative to other nations. Herein, we conducted a large population-based observational cohort study of adult residents of Ontario (Canada) with normal baseline kidney function to compare longitudinal adverse kidney outcomes between immigrants and non-immigrants.

METHODS

Study Design and Setting

This was a population-level, observational cohort study of adult (≥18 years of age) residents of Ontario, Canada with normal baseline kidney function (outpatient eGFR ≥70mL/min/1.73m^2) which was conducted using linked databases held at ICES (formerly, Institute for Clinical Evaluative Sciences). Ontario is Canada's largest province with over 15 million residents.[33] ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. The reporting of this study follows guidelines for observational studies (**Supplementary Table S1**).[34, 35]

Data Sources

Baseline characteristics and outcome data were ascertained from de-identified, linked databases housed at ICES. Demographic and vital status information was obtained from the Ontario Registered Persons Database. Immigrant-specific information was captured for all immigrants to Ontario in the Immigration, Refugees and Citizenship Canada (IRCC) Permanent Resident Database.[36] Diagnostic and procedural information from all hospitalizations was collected using the Canadian Institute for Health Information Discharge Abstract Database. Diagnostic information from emergency room and day surgery visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan (OHIP) database, which contains all health claims for inpatient and outpatient physician services. Dialysis and kidney transplant information was obtained from the Canadian Organ Replacement Registry. Laboratory information is contained in the Ontario Laboratory Information System (OLIS) which captures laboratory tests for all patients in Ontario.

Definitions for patient characteristics and clinical variables can be found in **Supplementary Table S2**. These datasets were linked using unique encoded identifiers and analyzed at ICES. The databases were complete for all variables used except for rural residence, neighborhood income quintile, and immigrant world region of origin, which were missing in <0.5% of individuals. The only reason for lost follow-up was emigration from the province which occurs in <0.5% of Ontario residents annually.[37]

Cohort Definition

All Ontario residents ≥18 years of age that had a single index outpatient eGFR measurement ≥70mL/min/1.73m^2 between April 1, 2007 and September 30, 2020 were included. The date of this initial eGFR measurement ≥70mL/min/1.73m^2 served as the study index date. Individuals were excluded if they had an outpatient eGFR <70 mL/min/1.73m^2 at index, a history of dialysis, or a history of kidney transplantation. The 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based equation was used to calculate eGFR. Individuals were followed from study index date until the outcome of interest or censoring. Censoring events included emigration from Ontario, death, or the end of study period.

Exposure

Individuals were compared based on whether they were a foreign-born immigrant Canadian citizen or a non-immigrant Canadian citizen by birth. All immigrants to Canada since 1985 are captured in the IRCC database upon arrival. Immigrants were further sub-classified based on whether they were a refugee versus non-refugee immigrant, they had a recent (2005-2020) versus remote (1985-2004) landing date, and the world region they immigrated to Canada from.

Outcomes

The primary outcome was a composite kidney outcome of 40% decline in eGFR or kidney

failure. Kidney failure was defined as initiation of maintenance dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation. For the 40% eGFR decline outcome, only outpatient eGFR measurements were included. Inpatient or emergency room eGFR measurements were not included so as to minimize the risk of capturing acute kidney injury (AKI) events. Secondary outcomes included evaluation of the individual components of the composite kidney outcome (40% eGFR decline and kidney failure) separately.

Statistical Analysis

Baseline characteristics were ascertained for immigrants and non-immigrants. Continuous variables were reported as mean (standard deviation [SD]) while categorical variables were reported as number (%). Crude incidence rates (events per 1,000 person-years) were calculated for immigrants and non-immigrants. Multivariable Cox proportional hazards modeling was used to measure the association between immigrant status and the primary (composite) and secondary (40% eGFR decline and kidney failure) outcomes. Models were adjusted for the following variables selected *a priori* based upon clinical knowledge and previous literature: age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery).[39] Additional multivariable Cox models compared the risk for adverse kidney outcomes between: A) refugee and non-refugee immigrants, B) immigrants with recent [2005-2020] and remote [1985-2004] landing dates, and C) immigrants who came to Canada from different world regions. We conducted all analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). 95% confidence intervals (CI) that did not overlap with 1.0 and two-sided p-values <0.05 were treated as statistically significant.

Sensitivity Analyses

Sensitivity analyses included: A) utilizing Fine-Gray subdistribution hazard models accounting

for the competing risk of death, and B) restricting the study cohort to those individuals with a urine albumin-to-creatinine ratio [UACR] within one year of index and adjusting for UACR within the regression models.

RESULTS

Baseline Characteristics

From a total of 12,007,777 Ontario residents with an eGFR measurement within the accrual period, 10,440,210 met the inclusion criteria and were included in the study cohort (**Figure 1**). The cohort consisted of 2,253,360 (22%) immigrants and 8,186,850 (78%) non-immigrants (**Table 1**). The mean (SD) age of the cohort was 45 (17) years with immigrants being marginally younger than non-immigrants. Females made up 54% of the cohort which was similar among both immigrants and non-immigrants. The mean (SD) baseline eGFR was 102 (16) mL/min/1.73m^2 with immigrants having marginally higher values than non-immigrants. Overall, immigrants tended to reside in neighborhoods with lower income levels and in non-rural rural locations. Immigrants also generally had less comorbid conditions than non-immigrants.

Immigrant-Specific Characteristics

Table 2 displays immigrant-specific characteristics within the cohort. The distribution of era of landing in Canada was fairly evenly spread except for the earliest years (1985-1989) which consisted of a lower number of immigrants. Immigrants came from all regions around the world with the largest proportion (49%) coming from Asia. Refugees comprised 17% of the immigrant population.

Incidence Rates of Adverse Kidney Outcomes by Immigrant Status

Table 3 displays the number of outcome events by immigrant status. A total of 46,168 immigrants (2.05%) and 369,892 non-immigrants (4.52%) developed the composite kidney outcome over the follow-up period. This translated into a crude incidence rate of 2.77 (95% CI

2.75-2.80) events per 1,000 person-years for immigrants compared to 5.96 (95% CI 5.94-5.98) events per 1,000 person-years for non-immigrants. The vast majority of the composite outcome was driven by 40% eGFR decline with a crude incidence rate of 2.77 (95% CI 2.74-2.79) events per 1,000 person-years for immigrants compared to 5.93 (95% CI 5.91-5.95) events per 1,000 person-years for non-immigrants. There were a total of 1,912 (0.08%) kidney failure events among immigrants compared to 10,970 (0.13%) kidney failure events among non-immigrants. This translated into a crude incidence rate of 0.11 (95% CI 0.11-0.12) events per 1,000 person-years for immigrants compared to 0.17 (95% CI 0.17-0.18) events per 1,000 person-years for non-immigrants.

Risk of Adverse Kidney Outcomes by Immigrant Status

Supplementary Table S3 displays the crude and multivariable adjusted hazard ratios for kidney outcomes by immigrant status; the adjusted cumulative incidence curves are shown in **Figure 2**. In the multivariable Cox regression models, immigrants experienced a 30% lower risk for the composite kidney outcome compared to non-immigrants (adjusted hazard ratio [aHR] 0.70 [95% CI 0.69-0.71]). This was primarily driven by the 40% eGFR decline outcome (aHR 0.70 [95% CI 0.69-0.71]). However, immigrants also experienced a 21% lower risk for incident kidney failure compared to non-immigrants (aHR 0.79 [95% CI 0.75-0.83]). The heightened risk for kidney failure was driven by an increased risk for requiring dialysis (aHR 0.79 [95% CI 0.75-0.83]) whereas there was no significant difference in risk for kidney transplantation (aHR 1.05 [95% CI 0.90-1.23]).

Risk of Adverse Kidney Outcomes among Refugee and Non-Refugee Immigrants

Supplementary Table S4 displays the crude and multivariable adjusted hazard ratios for kidney outcomes based on refugee versus non-refugee immigrant status. Both refugees (aHR 0.80 [95% CI 0.79-0.82]) and non-refugees (aHR 0.68 [95% CI 0.67-0.69]) experienced a lower risk for the composite kidney outcome compared to non-immigrants, which was predominantly

driven by a lower risk for 40% eGFR decline. While non-refugee immigrants experienced a lower risk of kidney failure compared to non-immigrants (aHR 0.76 [95% CI 0.72-0.81]), there was no significant difference in kidney failure risk between refugee immigrants and non-immigrants (aHR 0.93 [95% CI 0.84-1.03]). When comparing refugee versus non-refugee immigrants directly, refugee immigrants experienced a 20% higher risk of both the composite kidney outcome and 40% eGFR decline (aHR 1.20 [95% CI 1.17-1.23]) along with a 26% higher risk of kidney failure (aHR 1.26 [95% CI 1.13-1.42]).

Risk of Adverse Kidney Outcomes among Immigrants by Landing Date

Supplementary Table S5 displays the crude and multivariable adjusted hazard ratios for kidney outcomes among immigrants with recent (2005-2020) versus remote (1985-2004) landing dates. Both recent (aHR 0.67 [95% CI 0.66-0.68]) and remote (aHR 0.71 [95% CI 0.70-0.72]) immigrants experienced a lower risk for the composite kidney outcome compared to non-immigrants, which was predominantly driven by a lower risk for 40% eGFR decline. Both recent (aHR 0.74 [95% CI 0.67-0.82]) and remote (aHR 0.81 [95% CI 0.76-0.85]) also experienced a lower risk of kidney failure compared to non-immigrants. When comparing recent versus remote immigrants directly, recent immigrants experienced a 6% lower risk of both the composite kidney outcome and 40% eGFR decline (aHR 0.94 [95% CI 0.92-0.96]) but no significant difference in the risk of kidney failure (aHR 0.92 [95% CI 0.82-1.03]).

Risk of Adverse Kidney Outcomes among Immigrants by World Region

Figure 3 displays the risk of adverse kidney outcomes for immigrants by world region. For the composite kidney outcome, immigrants from all world regions experienced a lower risk compared to non-immigrants with a progressively lower risk among immigrants from North America (aHR 0.88 [95% CI 0.86-0.90]), Africa (aHR 0.84 [95% CI 0.81-0.87]), South America (aHR 0.84 [95% CI 0.81-0.87]), Middle East (aHR 0.78 [95% CI 0.75-0.80]), Europe (aHR 0.73 [95% CI 0.72-0.75]), and Asia (aHR 0.60 [95% CI 0.59-0.61]) which was predominantly driven

by a lower risk for 40% eGFR decline. Immigrants from the Middle East (aHR 0.60 [95% CI 0.49-0.73]), Europe (aHR 0.63 [95% CI 0.56-0.71]), and Asia (aHR 0.78 [95% CI 0.72-0.83]) experienced a lower risk for kidney failure compared to non-immigrants. There was no significant difference in kidney failure risk for immigrants from North America (aHR 1.05 [95% CI 0.94-1.18]), Africa (aHR 0.94 [95% CI 0.80-1.10]), or South America (aHR 0.88 [95% CI 0.74-1.05]) compared to non-immigrants.

Additional Analyses

When incorporating Fine-Gray subdistribution hazard modeling to treat death as a competing (rather than censoring) event, results were similar for the primary analysis of the association between immigrant status (immigrants versus non-immigrants) and the composite kidney outcome (aHR 0.70 [95% CI 0.69-0.71]). When adjusting for baseline UACR in the subset of individuals with UACR measurements within one year of index (n = 5,831 immigrants, n = 25,461 non-immigrants), the results still remained consistent in the association between immigrant status and the composite kidney outcome (aHR 0.74 [95% CI 0.69-0.80]).

DISCUSSION

In this large population-based cohort study of Canadian adults with normal baseline kidney function, we found that immigrants experienced a lower risk for adverse kidney outcomes including 40% eGFR decline and incident kidney failure compared to non-immigrants. The lower risk for adverse kidney outcomes was consistent among both refugee and non-refugee immigrants but more pronounced among non-refugee immigrants. The lower risk was also consistent among immigrants with recent and remote landing dates; however, the risk was lowest among immigrants with more recent landing dates. Immigrants from all world regions experienced a lower risk for adverse kidney outcomes compared to non-immigrants; however, the magnitude of risk reduction varied significantly by world region.

These findings extend the results of prior work demonstrating a healthy immigrant effect whereby immigrants hold a health advantage over their domestic-born peers.[21-26] This effect has been demonstrated in other chronic health conditions including as cardiovascular disease, diabetes mellitus, and dementia.[21-25] The present study now extends the healthy immigrant effect to include kidney disease. The healthy immigrant effect is postulated to relate to healthier lifestyle behaviors among immigrants as compared to non-immigrants including increased physical activity, a diet comprised of more fruits and vegetables with less highly processed foods, lower smoking rates, and lower levels of alcohol intake.[23, 24, 27-29] Additionally, the immigration process itself may further contribute to the healthy immigrant effect for several reasons. First, healthier individuals are more likely to pursue immigration than their less healthy counterparts.[40, 41] Second, the medical screening tests required as part of most immigration processes may further exclude less healthy individuals as potential immigrants. Third, the immigration processes for many countries (including Canada) place a high value on factors such as the education level and language skills for immigrants,[26, 42] social factors which not only promote successful employment post-immigration, but also are linked to improved kidney (and overall) long-term health.[10, 11, 13] Notably, the healthy immigrant effect has previously been shown to wane over time for other chronic health conditions which is postulated to occur in a gradual fashion as immigrants adapt to the lifestyle habits of their new living environment.[29, 43, 44] Similarly, we found that risk reduction for adverse kidney outcomes was greatest for immigrants with more recent landing dates and reduced for immigrants with more remote landing dates.

Previous literature on the link between immigrant status and kidney disease has yielded conflicting results. A notable limitation of these studies is that they primarily focused on prevalent, rather than incident, kidney disease thereby making it uncertain of whether their findings signified differences in kidney disease progression or simply the inherent makeup of the immigrant population accepted into that country. For instance, a study from the United States using National Health and Nutrition Examination Survey (NHANES) data found similar results to

the present study with immigrants experiencing 25% lower odds for having prevalent CKD (defined as an eGFR <60 mL/min/1.73m^2) compared to non-immigrants.[30] Also consistent with the present study, the NHANES data demonstrated a waning of the healthy immigrant effect as the length of residence in the United States increased. On the other hand, a prior study from Ontario, Canada (same location as the present study) found that the age-adjusted prevalence of end-stage kidney disease (ESKD) requiring dialysis was 29% higher among immigrants compared to long-term Canadian residents.[31] The difference in results between these studies in the same geographical location likely reflects the inherent challenges with comparing studies of prevalent kidney versus incident disease. By studying prevalent ESKD, the prior study likely captured a disproportionate number of immigrants with pre-existing CKD or ESKD who immigrated to Canada relative to non-immigrants. In the present study design, such individuals would have been excluded. We now show that among immigrants who enter Canada with normal baseline kidney function, their risk for kidney disease progression and incident CKD is actually lower than non-immigrants.

Several notable findings from this study relate to relevant details about how and from where immigrants arrived to Canada. While both refugee and non-refugee immigrants had a lower risk for adverse kidney outcomes relative to non-immigrants, kidney outcomes were worse for refugee immigrants compared to non-refugee immigrants. Refugees are displaced individuals who have been forced to relocate to another country for reasons such as war, natural disasters, or economic crises. While close attention has historically been paid to communicable illnesses potentially carried by refugees, an often overlooked aspect of refugee health is non-communicable illnesses (many of which predispose to kidney disease) which are common and may have been missed or poorly controlled for an extended period of time. Moreover, differential risks for adverse kidney outcomes were seen based upon what region of the world an immigrant relocated to Canada from. Immigrants from North America experienced the most similar risk for adverse kidney outcomes relative to non-immigrants. These immigrants may be

most similar to native-born Canadians not only geographically but also health behavior-wise. The next world region with the least reduction in adverse kidney outcome risk relative to non-immigrants was Africa. This may relate not only to traditional kidney disease risk factors but also poor access to health care, low health literacy, and genetic predisposition (e.g., APOL1 and sickle cell disease).[47-49]

Future research is needed to better understand the reasons behind why immigrants experience a lower rate of adverse kidney outcomes. This should entail evaluation of longitudinal trends in CKD-predisposing health conditions (e.g., diabetes, hypertension), lifestyle behaviors (e.g., diet, exercise, smoking), and social determinants of health (e.g., education, employment, housing stability) to identify areas for intervention. An enhanced appreciation for how these factors vary by immigrant type (e.g., refugee status, country of origin, etc.) will allow for more targeted screening strategies and more cost-effective resource allocation.

The strengths and novelty of this study include a large, population-based cohort in a geographical location (Canada) where immigrants are provided universal health care coverage soon after landing, thus minimizing access to health care as a barrier. However, the findings must be interpreted within the context and limitations of the study design. First, given the observational study design, only association but not causation was evaluated. The statistical models accounted for numerous known potential confounders in order to reduce observed confounding; however, unobserved confounding may still have occurred. Second, kidney disease is defined not only by a reduction in eGFR but also by albuminuria. Notably, a sensitivity analysis adjusting for albuminuria among the subset of individuals with available UACR measures within one year of index were consistent with the primary analysis. Third, medication data in Ontario is available only for individuals ≥65 years of age as this is the age at which universal drug coverage is provided. As most individuals in the cohort were <65 years of age, we were unable to adjust for medications that may impact kidney function (e.g., renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors, etc.)

within our models. Finally, the IRCC database captures 100% of immigrants to Canada from 1985 onwards. Therefore, we were unable to distinguish between individuals who were born in Canada and long-term residents who immigrated to Canada before 1985. This misclassification could potentially have attenuated the magnitude of the associations between immigrant status and adverse kidney outcomes.

In summary, this large population-based observational cohort study found that immigrants to Canada with normal baseline kidney function experienced a lower risk of both 40% eGFR decline and kidney failure compared to non-immigrants. As has been demonstrated with other chronic diseases, these findings suggest that a healthy immigrant effect also extends to kidney disease. Notably, differential kidney disease risks were identified among immigrants based on refugee status, date of landing, and world region of origin which may inform health policy decision-making toward targeted screening and cost-effective resource allocation for immigrant populations.

DISCLOSURE STATEMENT

AA reports receiving speaker fees from AstraZeneca and holds research grants from Otsuka, all outside of the submitted work. MMS reports receiving speaker fees from AstraZeneca, Otsuka, Bayer, and GlaxoSmithKline, all outside of the submitted work. All remaining authors declared no competing interests.

CHAPTER 5: THESIS DISCUSSION

Summary of results

In this population-based cohort of Ontario adults, this thesis assesses the spectrum of CKD in Canadian immigrants compared to native-born non-immigrants, using linked databases held at ICES (previously known as the Institute for Clinical Evaluative Sciences). In **Chapter 2,** a brief background on the social determinants of health in chronic kidney disease (CKD) is presented. This is followed up by **Chapter 3 (Manuscript I)** in which we determine the incidence of chronic kidney disease in Canadian immigrants relative to non-immigrants. In **Chapter 4** we assess the more severe forms of kidney disease, specifically a 40% or greater reduction in eGFR and kidney failure, in the immigrant vs. non-immigrant populations. Both Chapter 3 and Chapter 4 also examine and contrast kidney disease between the subtypes of immigrants (refugees and non-refugees) and immigrant world-region of origin. **Chapter 5** will focus on significant findings presented in this thesis, limitations of the two main studies as well as future directions for research.

Key findings

Generally, we found that Canadian immigrants had a lower incidence of CKD compared to non-immigrants, and this persisted regardless of whether an immigrant was a refugee or not and across each sensitivity analysis. The incident risk of CKD differed by immigrant world region of origin, specifically it was lowest in immigrants from Asia and Pacific and was highest in immigrants originating from North America (immigrants from Africa were a close second).

In **Manuscript I**, we saw that immigrants experienced a 20% reduced risk for incident CKD compared to non-immigrants (adjusted hazard ratio [HR] 0.80 [95% CI 0.80-0.81]). The primary outcome in this study was a single eGFR <60mL/mg/m^2 because it has been found to be a strong surrogate marker of CKD (3). However, since the clinically accepted KDIGO definition of CKD is an eGFR <60mL/mg/m^2 persisting for 3 months or more, we redefined incident CKD as

two measures of eGFR<60 within 90 days of each other as a sensitivity analysis and observed very similar results. This trend of reduced CKD risk in immigrants persisted after utilizing Fine-Gray substitution (as opposed to treating death as a censorship event in the primary analysis) as well within the sub-cohort of individuals controlling for urine ACR, another measurement used in conjunction with eGFR to diagnose CKD. Additionally, refugee and non-refugee immigrants both saw reduced CKD risk relative to non-immigrants but when comparing refugee and non-refugee immigrants to each other, refugees had elevated CKD risk (adjusted HR 1.11 [1.09-1.12.

In **Manuscript II** we found that immigrants experienced a 30% lower risk of our composite ESKD outcome (aHR 0.70, 95% CI [0.68-0.71]) than non-immigrants. This trend persisted regardless of whether an immigrant was a refugee (adjusted HR 0.80 [95% CI 0.79-0.82]) or a non-refugee (aHR 0.68, 95% CI 0.67-0,69) (where non-immigrant is reference). However, again, refugees had a higher risk of severe kidney disease. than non-refugees (adjusted HR 1.20 [95% CI 1.17-1.23]). When assessing these severe kidney disease outcomes individually we see that immigrants had a lower risk of a 40% reduction in eGFR and a lower risk of kidney failure compared to non-immigrants. Comparing refugee to non-refugee immigrants we saw that severe CKD risk is higher in refugees.

In both manuscript I and manuscript II we found that immigrants originating from North America and Africa were closest in disease risk to non-immigrants, while immigrants originating from every other part of the world had significant reductions in risk compared to non-immigrant Canadians. Specifically, immigrants from North America were not statistically different in risk of an eGFR<60mL/mg/min^2 (aHR 0.99, 95% CI 0.97-1.01, manuscript I) and kidney failure (aHR 0.97, 95% CI 0.95-0.99, manuscript II) compared to non-immigrant Canadians. Immigrants originating from Africa were second closest to non-immigrant Canadians in risk of an eGFR<60mL/mg/min^2 (aHR 0.97, 95% CI 0.95-0.99) and were not statistically different in risk of kidney failure from non-immigrant Canadians (aHR 0.94, 95% CI 0.80-1.10). Both recent

(landed in Canada 2005-2020) and remote (landed in Canada 1985-2004) immigrants had reduced risk of both an eGFR<60mL/mg/min^2 and each severe kidney disease outcome (composite kidney outcome, 40% eGFR decline, and kidney failure) compared to non-immigrants. However, remote immigrants had greater disease risk in each severe kidney disease outcome compared to recent suggesting that the healthy immigrant effect wears off with duration of stay in destination country.

Study Significance

The current thesis reveals that being a Canadian immigrant is associated with a significant reduction in risk of incident CKD and ESKD, therefore suggesting a "Healthy Immigrant Effect". This is consistent with previous studies also finding that non-immigrants are more susceptible to chronic diseases than the native-born individuals of their destination country (14,23,34). The "Healthy Immigrant effect" is thought to occur due to healthier lifestyle behaviors among immigrants compared to their native-born counterparts, including a diet consisting of more vegetables and fruits with less highly processed foods, greater physical activity levels, lower alcohol intake levels, and lower smoking rates (9,14,36) Moreover, the immigration process itself may contribute to the healthy immigrant effect. Healthier individuals are more likely to pursue immigration than those with waning health. The Canadian immigration system requires immigrant applicants to have several medical tests to ensure good health of potential incoming immigrants in an effort to prevent further strain on the healthcare system that comes with treating chronic diseases (37). Amongst these medical tests, Immigrant applicants aged 15 years and older must complete routine blood testing for serum creatinine to detect kidney disease (37,38). This serum creatinine testing likely dissuades individuals with kidney complications from immigrating into Canada making the incoming immigrant population overall healthier than non-immigrants who are not asked to take this screening test, supporting our study findings. Additionally, Canada's immigration point system selects individuals on the basis of human capital; higher education and language skills that will ensure employment post-

migration are typically associated with improved kidney (and overall) health (14,33,39,40).

Immigrants originating from North America likely had kidney disease risk similar to that of a non-immigrant due to similar lifestyle factors, such as diet, exercise levels, drinking and smoking habits etc., Immigrants originating from Africa likely had kidney disease risk close to that of a non-immigrant thanks to their genetic predisposition. People who lived in Western and Central Africa were prone to develop a genetic mutation in the APOL1 gene that protected them against certain types of parasites that induce African Sleeping Sickness, but also makes them more susceptible to kidney disease (41).

Our findings contrast with a previous population study assessing ESKD among Ontario immigrants which found ESKD to be more common in immigrants than non-immigrants (age-adjusted prevalence ratio 1.29, 95% CI 1.23 to 1.26; long-term Canadian residents serve as reference group). However, a notable limitation on previous research on North American Immigrant vs. long-term resident CKD is that past studies focused on kidney disease prevalence as opposed to incidence. By examining a cohort of immigrants with normal kidney function early upon arrival to Canada, we isolate the effect of immigration to Canada and its related changes on lifestyle, diet and health. These results can help inform health policies, influencing the medical screening practices to mandate long-term residents of Canada and non-immigrants to be extra vigilant with routine screening for CKD in order to catch the disease earlier than later for optimal health outcomes during treatment. Sickle cell disease is also predominant in individuals of West African descent; the reduced blood flow to the kidneys as a result of sickled cells can lead to kidney damage (42)

Limitations

The present thesis has several strengths such as a significantly large population-based cohort of over 10 million individuals and a focus on kidney disease incidence as opposed to prevalence. Additionally, since the study is based in Canada, immigrants are provided universal

health care coverage shortly after landing, thus minimizing variation in regard to levels of access to healthcare. However, there are also several limitations. Firstly, one must be mindful that since this is a retrospective-cohort study only associations can be drawn, not causation. Secondly, the results of this study may not generalize to countries beyond Canada. Canada's universal health care, quality of healthcare delivery, and immigration point-system/policies may not be easily generalized to just any other country due to its uniqueness. Thirdly, despite controlling for many known potential confounding factors, medication data in Ontario is only available for adults ≥65 years old because this is the age at which the province provides universal drug coverage. Since most people in the study cohort are ≤65 years of age, we were unable to adjust for medications that could potentially influence kidney function (e.g., sodium-glucose cotransporter-2 inhibitors, renin-angiotensin-aldosterone system inhibitors, etc.,) within our regression models. We controlled for factors we knew were associated with both immigrant status and kidney function, however, there may be residual confounding factors not available in ICES that we did not account for. Finally, as aforementioned within manuscript I and II, kidney disease is not solely defined by a reduction in eGFR, albuminuria is often an indicator used in conjunction with eGFR to accurately diagnose individuals with the disease. We employed sensitivity analyses with a sub-cohort of individuals who had a urine albumin-to-creatinine ratio (UACR) measurement within one year of index and adjusted for UACR to compensate for this.

Future Directions

The current thesis opens several potential future directions for research within this study population as well as efforts to spearhead early prevention of CKD to improve public health. Firstly, more research into the lifestyle factors that induce the healthy immigrant effect (i.e., physical activity levels, diet, reduced smoking) perhaps before and after landing is needed to shed further light on the phenomenon. Secondly, more studies on the duration of the healthy immigrant effect, especially varying by world region of origin are needed to aid in informing health recommendations for incoming immigrants. Thirdly, we only controlled for income on a

neighborhood level at baseline, but it is likely that an individual immigrant's income can vary significantly the longer they remain in the destination country. In the future we could possibly assess kidney disease risk in Canadian immigrants vs. non-immigrants where the individual incomes of a sample are collected every 5 years an individual has resided in the destination country. Fourthly, considering the lack of effect refugee vs non-refugee status played in disease risk, but the significant variation due to world region of origin, future studies could further break down world region of origin by refugee status to assess any subgroup effects. Finally, future research should examine longitudinal trends on the association between illnesses that pre-dispose to CKD such as diabetes, hypertension, and cardiovascular disease

Conclusion

In this thesis examining a population-based cohort of over 10.4 million adults, we found that Canadian immigrants have a lower incidence of CKD and a lower risk of CKD progression compared to non-immigrants. The lower risk of CKD persisted regardless of immigrant landing date and regardless of whether an immigrant was a refugee or not. North America was the only world region of origin where immigrants to Canada did not differ from non-immigrants in risk of an eGFR<60mL/min/1.73m^2. Both North America and Africa were the only two world regions of origin where immigrants to Canada did not differ from non-immigrants in risk of kidney failure. These findings will emphasize the need for more targeted health screening practices and lifestyle recommendations to aid in catching kidney disease in its early stages to improve prognoses.

REFERENCES

1. A S Levey. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007 Aug;

2. kidney.ca. https://kidney.ca/KFOC/media/images/PDFs/Facing-the-Facts-2020.pdf. 2020. Facing the Facts.

3. Bikbov B, Purcell C, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020 Feb 29;395(10225):709–33.

4. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO) [Internet]. Vol. 67, Kidney International. 2005. Available from: www.kdigo.org.

5. Blazek O, Bakris GL. Slowing the Progression of Diabetic Kidney Disease. Vol. 12, Cells. Multidisciplinary Digital Publishing Institute (MDPI); 2023.

6. Ammirati AL. Chronic kidney disease. Vol. 66, Revista da Associacao Medica Brasileira. Associacao Medica Brasileira; 2020. p. 3–9.

7. Shokeen D, Wang N, Nguyen NP, Bakal E, Tripathi O, Palaniappan LP, et al. The association between local area immigrant fraction and prevalence of cardiovascular diseases in the United States: an observational study. The Lancet regional health. 2023;27:100613.

8. Fang J, Yuan K, Gindi RM, Ward BW, Ayala C, Loustalot F. Association of Birthplace and Coronary Heart Disease and Stroke Among US Adults: National Health Interview Survey, 2006 to 2014. J Am Heart Assoc. 2018;7(7).

9. Shi L, Zhang D, Rajbhandari-Thapa J, Katapodis N, Su D, Li Y. Neighborhood immigrant density and population health among native-born Americans. Prev Med (Baltim). 2019;127:105792.

10. Tu J V, Chu A, Rezai MR, Guo H, Maclagan LC, Austin PC, et al. The Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. Circulation. 2015;132(16):1549–1559.

11. Quiñones J, Hammad Z. Social Determinants of Health and Chronic Kidney Disease. Cureus. 2020;12(9):e10266.

12. Chang CD. Social Determinants of Health and Health Disparities Among Immigrants and their Children. Curr Probl Pediatr Adolesc Health Care. 2019 Jan 1;49(1):23–30.

13. Statistics Canada. Population Estimates, quarterly [Internet]. 2024 [cited 2024 Mar 31]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000901

14. Vang ZM, Sigouin J, Flenon A, Gagnon A. Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. Ethn Health. 2017;22(3):209–41.

15. Perl J, McArthur E, Tan VS, Nash DM, Garg AX, Harel Z, et al. ESRD among Immigrants to Ontario, Canada: A Population-Based Study. Journal of the American Society of Nephrology [Internet]. 2018 Jul 1 [cited 2024 Mar 3];29(7):1948–59. Available from: https://journals.lww.com/jasn/fulltext/2018/07000/esrd_among_immigrants_to_ontario,_canada_a.19.aspx

16. Levey AS, De Jong PE, Coresh J, Nahas M El, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28.

17. Chang CD. Social Determinants of Health and Health Disparities Among Immigrants and their Children. Curr Probl Pediatr Adolesc Health Care. 2019;49(1):23–30.

18. Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V, et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. In: Kidney International. Elsevier B.V.; 2021. p. 34–47.

19. Kitzler TM, Chun J. Understanding the Current Landscape of Kidney Disease in Canada to Advance Precision Medicine Guided Personalized Care. [cited 2024 Mar 3]; Available from: https://doi.org/10.1177/20543581231154185

20. U.S Centers for Disease Control and Prevention. Chronic Kidney Disease Basics. 2024.

21. Thomas B, MK, AKH, AAZ, ÄJ, AK, AR, BA, BSH, BA, BL, BCE, BS, BAK, BI, BJ, BB, B et al. ,. Global Cardiovascular and Renal Outcomes of Reduced GFR. Journal of the American Society of Nephrology. 2017 Jul;28(7):2167–79.

22. Ontario.ca. King's Printer for Ontario, 2012-24. 2024. Ontario Demographic Quarterly: Highlights of third quarter.

23. Jeffrey Perl EMVSTDMNAXGZHAHLMMSJGRRW. ESRD among Immigrants to Ontario, Canada: A Population-Based Study. Journal of the American Society of Nephrology. 2018 Jul;29(7):1948–59.

24. Gagnon M, Kansal N, Goel R, Gastaldo D. Immigration Status as the Foundational Determinant of Health for People Without Status in Canada: A Scoping Review. Vol. 24, Journal of Immigrant and Minority Health. Springer; 2022. p. 1029–44.

25. colpitts-freitag-1997-organ-donation-and-transplantation-in-the-canadian-healthcare-system.

26. Tonelli M, Wiebe N, Joanette Y, Hemmelgarn BR, So H, Straus S, et al. Age, multimorbidity and dementia with health care costs in older people in Alberta: a population-based retrospective cohort study. CMAJ Open. 2022 Jul 1;10(3):E577–88.

27. Adjei JK, Adu PA, Ackah BBB. Revisiting the healthy immigrant effect with diabetes risk in Canada: why race/ethnicity matters. Ethn Health. 2020 May 18;25(4):495–507.

28. Okrainec K, Bell CM, Hollands S, Booth GL. Risk of cardiovascular events and mortality among a population-based cohort of immigrants and long-term residents with diabetes: Are all immigrants healthier and if so, for how long? Am Heart J. 2015 Jul 1;170(1):123–32.

29. Dawson AZ, Garacci E, Ozieh M, Walker RJ, Egede LE. The Relationship Between Immigration Status and Chronic Kidney Disease Risk Factors in Immigrants and US-Born Adults. J Immigr Minor Health. 2020 Dec 1;22(6):1200–7.

30. Wandell P, Carlsson AC, Li X, Gasevic D, Ärnlöv J, Sundquist J, et al. End-Stage Kidney Diseases in Immigrant Groups: A Nationwide Cohort Study in Sweden. Am J Nephrol. 2019 Mar 1;49(3):186–92.

31. James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. Vol. 375, The Lancet. Elsevier B.V.; 2010. p. 1296–309.

32. Markides KS, Rote S. The Healthy Immigrant Effect and Aging in the United States and Other Western Countries. Gerontologist. 2019;59(2):205–14.

33. Clark-Cutaia MN, Rivera E, Iroegbu C, Squires A. Disparities in chronic kidney disease-the state of the evidence. Vol. 30, Current Opinion in Nephrology and Hypertension. Lippincott Williams and Wilkins; 2021. p. 208–14.

34. Kim H, Cao C, Grabovac I, López Sánchez GF, Rana B, Jacob L, et al. Associations in physical activity and sedentary behaviour among the immigrant and non-immigrant US

population. J Epidemiol Community Health (1978). 2020;74(8):655–61.

35. Choi AI, Weekley CC, Chen SC, Li S, Kurella Tamura M, Norris KC, et al. Association of educational attainment with chronic disease and mortality: the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2011;58(2):228–34.

36. Morton RL, Schlackow I, Staplin N, Gray A, Cass A, Haynes R, et al. Impact of Educational Attainment on Health Outcomes in Moderate to Severe CKD. Am J Kidney Dis. 2016;67(1):31–9.

37. Hundemer GL, Ravani P, Sood MM, Zimmerman D, Molnar AO, Moorman D, et al. Social determinants of health and the transition from advanced chronic kidney disease to kidney failure. Nephrology Dialysis Transplantation. 2023 Jul 1;38(7):1682–90.

REFERENCES

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl (2011)* 2022;12(1):7-11. doi: 10.1016/j.kisu.2021.11.003 [published Online First: 2022/05/10]

2. Kitzler TM, Chun J. Understanding the Current Landscape of Kidney Disease in Canada to Advance Precision Medicine Guided Personalized Care. *Can J Kidney Health Dis* 2023;10:20543581231154185. doi: 10.1177/20543581231154185 [published Online First: 2023/02/18]

3. Wesson L. Physiology of the human kidney. New York: Grune & Stratton 1969.

4. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351(13):1296-305. doi: 10.1056/NEJMoa041031 [published Online First: 2004/09/24]

5. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019;322(13):1294-304. doi: 10.1001/jama.2019.14745 [published Online First: 2019/10/02]

6. Hall YN. Social Determinants of Health: Addressing Unmet Needs in Nephrology. *Am J Kidney Dis* 2018;72(4):582-91. doi: 10.1053/j.ajkd.2017.12.016 [published Online First: 2018/03/20]

7. Norris KC, Beech BM. Social Determinants of Kidney Health: Focus on Poverty. *Clin J Am Soc Nephrol* 2021;16(5):809-11. doi: 10.2215/CJN.12710820 [published Online First: 2021/01/15]

8. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social Determinants of Racial Disparities in

CKD. *J Am Soc Nephrol* 2016;27(9):2576-95. doi: 10.1681/ASN.2016010027 [published Online First: 2016/05/15]

9. Volkova N, McClellan W, Klein M, et al. Neighborhood poverty and racial differences in ESRD incidence. *J Am Soc Nephrol* 2008;19(2):356-64. doi: 10.1681/ASN.2006080934 [published Online First: 2007/12/07]

10. Crews DC, McClellan WM, Shoham DA, et al. Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. *Am J Kidney Dis* 2012;60(5):779-86. doi: 10.1053/j.ajkd.2012.05.010 [published Online First: 2012/06/15]

11. Bruce MA, Beech BM, Crook ED, et al. Association of socioeconomic status and CKD among African Americans: the Jackson Heart Study. *Am J Kidney Dis* 2010;55(6):1001-8. doi: 10.1053/j.ajkd.2010.01.016 [published Online First: 2010/04/13]

12. Hall YN, Choi AI, Chertow GM, et al. Chronic kidney disease in the urban poor. *Clin J Am Soc Nephrol* 2010;5(5):828-35. doi: 10.2215/CJN.09011209 [published Online First: 2010/03/05]

13. Hall YN, Choi AI, Himmelfarb J, et al. Homelessness and CKD: a cohort study. *Clin J Am Soc Nephrol* 2012;7(7):1094-102. doi: 10.2215/CJN.00060112 [published Online First: 2012/06/16]

14. Patzer RE, Amaral S, Wasse H, et al. Neighborhood poverty and racial disparities in kidney transplant waitlisting. *J Am Soc Nephrol* 2009;20(6):1333-40. doi: 10.1681/ASN.2008030335 [published Online First: 2009/04/03]

15. Choi AI, Weekley CC, Chen SC, et al. Association of educational attainment with chronic disease and mortality: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2011;58(2):228-34. doi: 10.1053/j.ajkd.2011.02.388 [published Online First: 2011/05/24]

16. Morton RL, Schlackow I, Staplin N, et al. Impact of Educational Attainment on Health Outcomes in Moderate to Severe CKD. *Am J Kidney Dis* 2016;67(1):31-9. doi: 10.1053/j.ajkd.2015.07.021 [published Online First: 2015/09/20]

17. Wesselman H, Ford CG, Leyva Y, et al. Social Determinants of Health and Race Disparities in Kidney Transplant. *Clin J Am Soc Nephrol* 2021;16(2):262-74. doi: 10.2215/CJN.04860420 [published Online First: 2021/01/30]

18. Hundemer GL, Ravani P, Sood MM, et al. Social determinants of health and the transition from advanced chronic kidney disease to kidney failure. *Nephrol Dial Transplant* 2023;38(7):1682-90. doi: 10.1093/ndt/gfac302 [published Online First: 2022/11/01]

19. Statistics Canada. 2021 Census of Population. https://www12.statcan.gc.ca/census-recensement/2021/as-sa/fogs-spg/page.cfm?topic=9&lang=E&dguid=2021A000011124

20. Chang CD. Social Determinants of Health and Health Disparities Among Immigrants and their Children. *Curr Probl Pediatr Adolesc Health Care* 2019;49(1):23-30. doi: 10.1016/j.cppeds.2018.11.009 [published Online First: 2019/01/01]

21. Shokeen D, Wang N, Nguyen NP, et al. The association between local area immigrant fraction and prevalence of cardiovascular diseases in the United States: an observational study. *Lancet Reg Health Am* 2023;27:100613. doi: 10.1016/j.lana.2023.100613 [published Online First: 2023/10/20]

22. Tu JV, Chu A, Rezai MR, et al. The Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. *Circulation* 2015;132(16):1549-59. doi: 10.1161/CIRCULATIONAHA.115.015345 [published Online First: 2015/09/02]

23. Fang J, Yuan K, Gindi RM, et al. Association of Birthplace and Coronary Heart Disease and Stroke Among US Adults: National Health Interview Survey, 2006 to 2014. *J Am Heart*

Assoc 2018;7(7) doi: 10.1161/JAHA.117.008153 [published Online First: 2018/03/30]

24. Shi L, Zhang D, Rajbhandari-Thapa J, et al. Neighborhood immigrant density and population health among native-born Americans. *Prev Med* 2019;127:105792. doi: 10.1016/j.ypmed.2019.105792 [published Online First: 2019/08/10]

25. Kim H, Cao C, Grabovac I, et al. Associations in physical activity and sedentary behaviour among the immigrant and non-immigrant US population. *J Epidemiol Community Health* 2020;74(8):655-61. doi: 10.1136/jech-2020-213754 [published Online First: 2020/04/27]

26. Statistics Canada. Table 17-10-0005-01 Population estimates on July 1, by age and gender

27. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]

28. https://www.canada.ca/en/immigration-refugees-citizenship/corporate/contact-ircc.html

29. Statistics Canada. Table 17-10-0022-01 Estimates of interprovincial migrants by province or territory of origin and destination, annual. [

30. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 2021;385(19):1737-49. doi: 10.1056/NEJMoa2102953 [published Online First: 2021/09/24]

31. Garg AX, Mamdani M, Juurlink DN, et al. Identifying individuals with a reduced GFR using ambulatory laboratory database surveillance. *J Am Soc Nephrol* 2005;16(5):1433-9. doi: 10.1681/ASN.2004080697 [published Online First: 2005/04/01]

32. Hirst JA, Montes MDV, Taylor CJ, et al. Impact of a single eGFR and eGFR-estimating equation on chronic kidney disease reclassification: a cohort study in primary care. *Br J*

Gen Pract 2018;68(673):e524-e30. doi: 10.3399/bjgp18X697937 [published Online First: 2018/07/05]

33. Denic A, Mathew J, Lerman LO, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med* 2017;376(24):2349-57. doi: 10.1056/NEJMoa1614329 [published Online First: 2017/06/15]

34. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter, Suppl* 2013;3:1-150.

35. Vang ZM, Sigouin J, Flenon A, et al. Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. *Ethn Health* 2017;22(3):209-41. doi: 10.1080/13557858.2016.1246518 [published Online First: 2016/11/05]

36. Chetty R, Stepner M, Abraham S, et al. The Association Between Income and Life Expectancy in the United States, 2001-2014. *JAMA* 2016;315(16):1750-66. doi: 10.1001/jama.2016.4226 [published Online First: 2016/04/12]

37. Duffey KJ, Gordon-Larsen P, Ayala GX, et al. Birthplace is associated with more adverse dietary profiles for US-born than for foreign-born Latino adults. *J Nutr* 2008;138(12):2428-35. doi: 10.3945/jn.108.097105 [published Online First: 2008/11/22]

38. McDonald JT, Kennedy S. Insights into the 'healthy immigrant effect': health status and health service use of immigrants to Canada. *Soc Sci Med* 2004;59(8):1613-27. doi: 10.1016/j.socscimed.2004.02.004 [published Online First: 2004/07/29]

39. de Castro AB, Hing AK, Lee NR, et al. Cohort profile: the Health of Philippine Emigrants Study (HoPES) to examine the health impacts of international migration from the Philippines to the USA. *BMJ Open* 2019;9(11):e032966. doi: 10.1136/bmjopen-2019-

032966 [published Online First: 2019/11/16]

40. Martinez-Cardoso AM, Geronimus AT. The Weight of Migration: Reconsidering Health Selection and Return Migration among Mexicans. *Int J Environ Res Public Health* 2021;18(22) doi: 10.3390/ijerph182212136 [published Online First: 2021/11/28]

41. Markides KS, Rote S. The Healthy Immigrant Effect and Aging in the United States and Other Western Countries. *Gerontologist* 2019;59(2):205-14. doi: 10.1093/geront/gny136 [published Online First: 2018/11/02]

42. McDonald JT, Kennedy S. Is migration to Canada associated with unhealthy weight gain? Overweight and obesity among Canada's immigrants. *Soc Sci Med* 2005;61(12):2469-81. doi: 10.1016/j.socscimed.2005.05.004 [published Online First: 2005/06/24]

43. Ng E, Pottie K, Spitzer D. Official language proficiency and self-reported health among immigrants to Canada. *Health Rep* 2011;22(4):15-23. [published Online First: 2012/02/23]

44. Dawson AZ, Garacci E, Ozieh M, et al. The Relationship Between Immigration Status and Chronic Kidney Disease Risk Factors in Immigrants and US-Born Adults. *J Immigr Minor Health* 2020;22(6):1200-07. doi: 10.1007/s10903-020-01054-x [published Online First: 2020/07/21]

45. Perl J, McArthur E, Tan VS, et al. ESRD among Immigrants to Ontario, Canada: A Population-Based Study. *J Am Soc Nephrol* 2018;29(7):1948-59. doi: 10.1681/ASN.2017101055 [published Online First: 2018/05/04]

46. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013;369(23):2183-96. doi: 10.1056/NEJMoa1310345 [published Online First: 2013/11/12]

MANUSCRIPT II REFERENCES

REFERENCES

1. Vanjani R, Reddy N, Giron N*, et al.* The Social Determinants of Health - Moving Beyond Screen-and-Refer to Intervention. *N Engl J Med* 2023; **389:** 569-573.

2. Norris KC, Beech BM. Social Determinants of Kidney Health: Focus on Poverty. *Clin J Am Soc Nephrol* 2021; **16:** 809-811.

3. Norton JM, Moxey-Mims MM, Eggers PW*, et al.* Social Determinants of Racial Disparities in CKD. *J Am Soc Nephrol* 2016; **27:** 2576-2595.

4. Volkova N, McClellan W, Klein M*, et al.* Neighborhood poverty and racial differences in ESRD incidence. *J Am Soc Nephrol* 2008; **19:** 356-364.

5. Crews DC, McClellan WM, Shoham DA*, et al.* Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. *Am J Kidney Dis* 2012; **60:** 779-786.

6. Bruce MA, Beech BM, Crook ED*, et al.* Association of socioeconomic status and CKD among African Americans: the Jackson Heart Study. *Am J Kidney Dis* 2010; **55:** 1001-1008.

7. Hall YN, Choi AI, Chertow GM*, et al.* Chronic kidney disease in the urban poor. *Clin J Am Soc Nephrol* 2010; **5:** 828-835.

8. Hall YN, Choi AI, Himmelfarb J*, et al.* Homelessness and CKD: a cohort study. *Clin J Am Soc Nephrol* 2012; **7:** 1094-1102.

9. Patzer RE, Amaral S, Wasse H*, et al.* Neighborhood poverty and racial disparities in kidney transplant waitlisting. *J Am Soc Nephrol* 2009; **20:** 1333-1340.

10. Choi AI, Weekley CC, Chen SC*, et al.* Association of educational attainment with chronic disease and mortality: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2011; **58:** 228-234.

11. Morton RL, Schlackow I, Staplin N*, et al.* Impact of Educational Attainment on Health Outcomes in Moderate to Severe CKD. *Am J Kidney Dis* 2016; **67:** 31-39.

12. Wesselman H, Ford CG, Leyva Y*, et al.* Social Determinants of Health and Race Disparities in Kidney Transplant. *Clin J Am Soc Nephrol* 2021; **16:** 262-274.

13. Hundemer GL, Ravani P, Sood MM*, et al.* Social determinants of health and the transition from advanced chronic kidney disease to kidney failure. *Nephrol Dial Transplant* 2023; **38:** 1682-1690.

14. Crews DC, Charles RF, Evans MK*, et al.* Poverty, race, and CKD in a racially and socioeconomically diverse urban population. *Am J Kidney Dis* 2010; **55:** 992-1000.

15. Crews DC, Jaar BG, Plantinga LC*, et al.* Inpatient hemodialysis initiation: reasons, risk factors and outcomes. *Nephron Clin Pract* 2010; **114:** c19-28.

16. Thanabalasingam SJ, Akbari A, Sood MM*, et al.* Social determinants of health and dialysis modality selection in patients with advanced chronic kidney disease: A retrospective cohort study. *Perit Dial Int* 2024**:** 8968608241234525.

17. Crews DC, Bello AK, Saadi G*, et al.* Burden, Access, and Disparities in Kidney Disease. *Kidney Med* 2019; **1:** 6-12.

18. Hall YN. Social Determinants of Health: Addressing Unmet Needs in Nephrology. *Am J Kidney Dis* 2018; **72:** 582-591.

19. Gagnon M, Kansal N, Goel R*, et al.* Immigration Status as the Foundational Determinant of Health for People Without Status in Canada: A Scoping Review. *J Immigr Minor*

Health 2022; **24:** 1029-1044.

20. Chang CD. Social Determinants of Health and Health Disparities Among Immigrants and their Children. *Curr Probl Pediatr Adolesc Health Care* 2019; **49:** 23-30.

21. Shokeen D, Wang N, Nguyen NP*, et al.* The association between local area immigrant fraction and prevalence of cardiovascular diseases in the United States: an observational study. *Lancet Reg Health Am* 2023; **27:** 100613.

22. Tu JV, Chu A, Rezai MR*, et al.* The Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. *Circulation* 2015; **132:** 1549-1559.

23. Fang J, Yuan K, Gindi RM*, et al.* Association of Birthplace and Coronary Heart Disease and Stroke Among US Adults: National Health Interview Survey, 2006 to 2014. *J Am Heart Assoc* 2018; **7**.

24. Shi L, Zhang D, Rajbhandari-Thapa J*, et al.* Neighborhood immigrant density and population health among native-born Americans. *Prev Med* 2019; **127:** 105792.

25. Kim H, Cao C, Grabovac I*, et al.* Associations in physical activity and sedentary behaviour among the immigrant and non-immigrant US population. *J Epidemiol Community Health* 2020; **74:** 655-661.

26. Vang ZM, Sigouin J, Flenon A*, et al.* Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. *Ethn Health* 2017; **22:** 209-241.

27. Chetty R, Stepner M, Abraham S*, et al.* The Association Between Income and Life Expectancy in the United States, 2001-2014. *JAMA* 2016; **315:** 1750-1766.

28. Duffey KJ, Gordon-Larsen P, Ayala GX*, et al.* Birthplace is associated with more

adverse dietary profiles for US-born than for foreign-born Latino adults. *J Nutr* 2008; **138:** 2428-2435.

29. McDonald JT, Kennedy S. Insights into the 'healthy immigrant effect': health status and health service use of immigrants to Canada. *Soc Sci Med* 2004; **59:** 1613-1627.

30. Dawson AZ, Garacci E, Ozieh M*, et al.* The Relationship Between Immigration Status and Chronic Kidney Disease Risk Factors in Immigrants and US-Born Adults. *J Immigr Minor Health* 2020; **22:** 1200-1207.

31. Perl J, McArthur E, Tan VS*, et al.* ESRD among Immigrants to Ontario, Canada: A Population-Based Study. *J Am Soc Nephrol* 2018; **29:** 1948-1959.

32. Statistics Canada. 2021 Census of Population. https://www12.statcan.gc.ca/census-recensement/2021/as-sa/fogs-spg/page.cfm?topic=9&lang=E&dguid=2021A000011124.

33. Statistics Canada. Table 17-10-0005-01 Population estimates on July 1, by age and gender. In

34. Benchimol EI, Smeeth L, Guttmann A*, et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; **12:** e1001885.

35. von Elm E, Altman DG, Egger M*, et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med* 2007; **45:** 247-251.

36. https://www.canada.ca/en/immigration-refugees-citizenship/corporate/contact-ircc.html.

37. Statistics Canada. Table 17-10-0022-01 Estimates of interprovincial migrants by province or territory of origin and destination, annual.

38. Inker LA, Eneanya ND, Coresh J*, et al.* New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 2021; **385:** 1737-1749.

39. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019; **322:** 1294-1304.

40. de Castro AB, Hing AK, Lee NR*, et al.* Cohort profile: the Health of Philippine Emigrants Study (HoPES) to examine the health impacts of international migration from the Philippines to the USA. *BMJ Open* 2019; **9:** e032966.

41. Martinez-Cardoso AM, Geronimus AT. The Weight of Migration: Reconsidering Health Selection and Return Migration among Mexicans. *Int J Environ Res Public Health* 2021; **18**.

42. Markides KS, Rote S. The Healthy Immigrant Effect and Aging in the United States and Other Western Countries. *Gerontologist* 2019; **59:** 205-214.

43. McDonald JT, Kennedy S. Is migration to Canada associated with unhealthy weight gain? Overweight and obesity among Canada's immigrants. *Soc Sci Med* 2005; **61:** 2469-2481.

44. Ng E, Pottie K, Spitzer D. Official language proficiency and self-reported health among immigrants to Canada. *Health Rep* 2011; **22:** 15-23.

45. Yun K, Hebrank K, Graber LK*, et al.* High prevalence of chronic non-communicable conditions among adult refugees: implications for practice and policy. *J Community Health* 2012; **37:** 1110-1118.

46. Arici M. Refugees with kidney disease: an increasing global challenge. *Nat Rev Nephrol* 2021; **17:** 366-367.

47. Parsa A, Kao WH, Xie D*, et al.* APOL1 risk variants, race, and progression of chronic

kidney disease. *N Engl J Med* 2013; **369:** 2183-2196.

48. Adjei DN, Stronks K, Adu D*, et al.* Chronic kidney disease burden among African migrants in three European countries and in urban and rural Ghana: the RODAM cross-sectional study. *Nephrol Dial Transplant* 2018; **33:** 1812-1822.

49. Umeukeje EM, Young BA. Genetics and ESKD Disparities in African Americans. *Am J Kidney Dis* 2019; **74:** 811-821.

SUPPLEMENTARY MATERIAL

Thesis Manuscript I and II Tables

Table 1. Baseline Characteristics of the Study Cohort

Table 1. Baseline Characteristics of the Study Cohort.

Characteristic	Overall	Immigrants	Non-Immigrants
N (%)	10,440,210	2,253,360 (22)	8,186,850 (78)
Age, Years, Mean (SD)	45 (17)	41 (14)	47 (18)
Sex, N (%)			
Female	5,589,599 (54)	1,224,262 (54)	4,365,337 (53)
Male	4,850,611 (46)	1,029,098 (46)	3,821,513 (47)
Baseline eGFR, mL/min/1.73m^2, Mean (SD)	102 (16)	107 (15)	101 (16)
Neighborhood Income Quintile, N (%)[a]			

Quintile 1 (Lowest)	2,053,854 (20)	627,826 (28)	1,426,028 (17)
Quintile 2	2,082,562 (20)	509,345 (23)	1,573,217 (19)
Quintile 3	2,084,203 (20)	452,378 (20)	1,631,825 (20)
Quintile 4	2,131,199 (20)	392,621 (17)	1,738,578 (21)
Quintile 5 (Highest)	2,054,481 (20)	266,216 (12)	1,788,265 (22)
Rural Residence, N (%)[b]	1,056,347 (10)	22,855 (1)	1,033,492 (13)
Comorbidities			
Arrhythmia, N (%)	82,672 (1)	6,616 (0)	76,056 (1)
Atrial Fibrillation, N (%)	83,937 (1)	4,546 (0)	79,391 (1)
CABG, N (%)	31,022 (0)	2,755 (0)	28,267 (0)
Chronic Liver Disease, N (%)	302,097 (3)	85,272 (4)	216,825 (3)
Congestive Heart Failure, N (%)	149,500 (1)	10,036 (0)	139,464 (2)
COPD, N (%)	652,206 (6)	44,495 (2)	607,711 (7)
Coronary Artery Disease, N (%)	593,164 (6)	67,956 (3)	525,208 (6)
Diabetes Mellitus, N (%)	903,071 (9)	162,089 (7)	740,982 (9)
Hypertension, N (%)	2,368,505 (23)	337,779 (15)	2,030,726 (25)
Ischemic Stroke, N (%)	45,886 (0)	3,904 (0)	41,982 (1)
Major Cancer, N (%)	382,878 (4)	39,324 (2)	343,554 (4)
Myocardial Infarction, N (%)	84,734 (1)	7,358 (0)	77,376 (1)

[a] Neighborhood income quintile missing in 33,911 individuals (0.3% of cohort).

[b] Rural defined as residing in a location with population <10,000, missing in 11,671 individuals (0.1% of cohort).

Abbreviations: CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2. Immigrant-Specific Characteristics

Table 2. Immigrant-Specific Characteristics.

Characteristic	
Year of Landing, N (%)	
1985-1989	186,525 (8)
1990-1994	350,155 (16)
1995-1999	321,800 (14)
2000-2004	402,574 (18)
2005-2009	368,099 (16)
2010-2014	318,394 (14)
2015-2020	305,813 (14)
World Region of Origin, N (%)[a]	
Africa	161,179 (7)
Asia	1,096,777 (49)
Europe	409,750 (18)
Middle East	198,349 (9)
North America	220,173 (10)
South America	114,297 (5)
Stateless	52,593 (2)
Immigrant Type	
Refugee, N (%)	373,387 (17)

Non-refugee, N (%)	1,879,973 (83)

[a] World region of origin missing for 242 individuals (0.01% of immigrants).

THESIS MANUSCRIPT I AND II FIGURES

Figure 1. Study Flowchart

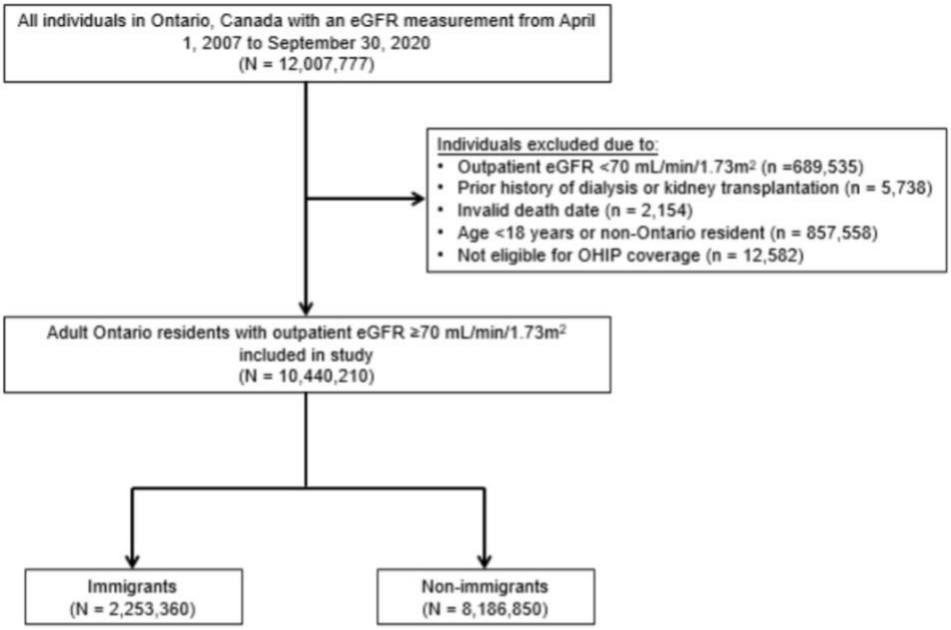


Figure 1

Abbreviations: eGFR, estimated glomerular filtration rate; OHIP, Ontario Health Insurance Plan.

THESIS MANUSCRIT I AND II SUPPLEMENTAL TABLE 1.

Supplemental Table 1. Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement checklist.

	Item No	STROBE items	RECORD items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	(1.1) The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. (1.2) If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. (1.3) If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction				
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Introduction
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. (6.2) Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. (6.3) If the study involved linkage of databases, consider use of a flow diagram or other graphical display to	Methods, Figure 1

			demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	(7.1) A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods, Supplemental Table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Methods
Bias	9	Describe any efforts to address potential sources of bias.		Methods
Study size	10	Explain how the study size was arrived at.		Methods, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		Methods
Data access and cleaning methods		N/A	(12.1) Authors should describe the extent to which the investigators had access to the database population used to create the study population. (12.2) Authors should provide information on the data cleaning methods used in the study.	Methods
Linkage		N/A	(12.3) State whether the study included person-level,	Methods

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		Results, Tables 1-2, Figures 2-3
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		Results, Supplemental Tables 3-5
Key results	18	Summarize key results with reference to study objectives.		Interpretation
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	(19.1) Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Interpretation
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Interpretation
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Interpretation
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		Funding
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

THESIS MANUSCRIPT I AND II SUPPLEMENTAL TABLE 2.

Supplemental Table 2. Databases and code definitions for patient characteristics and clinical variables.

Variable	Database	Codes
eGFR	Ontario Laboratory Information System (OLIS)	Observation code=14682-9
Age	Registered Persons Database (RPDB)	BDATE
Dialysis	Canadian Organ Replacement Register (CORR)	Recipient_Treatment database Treatment_Code≠ 171, 181
Kidney transplantation	CORR	Recipient_Treatment database Treatment_Code= 171, 181
Serum creatinine	OLIS	Observation code= 14682-9
Death	RPDB	DTH
Diabetes mellitus	Ontario Diabetes Dataset (ODD) Ontario Health Insurance Plan (OHIP) Discharge Abstract Database (DAD)	2 OHIP dxcode 250 claims or 1 DAD admission within 1 year after 19th birthday
Hypertension	Ontario Hypertension Dataset (HYPER) OHIP	Use diagnosis before index date: One hospital admission/SDS record with a hypertension diagnosis, ICD 9 dxcodes: 401x, 402x, 403x, 404x, 405x, ICD 10 dx10codes: I10, I11, I12, I13, I15, or - An OHIP claim with a hypertension diagnosis followed by either an OHIP claim or a hospital admission/SDS record with a hypertension diagnosis within two years. OHIP dxcodes: 401, 402, 403, 404, or 405
Neighbourhood Income	PCCF (Postal Code Conversion File)	Calculated using Census dissemination area and statistics Canada data
Rural Residence	RPDB	Determined using Census Postal Code data
Major Cancer	Canadian Institute for Health Information (CIHI) DAD National Ambulatory Care Reporting System (NACRS) OHIP	ICD10: 971, 980, 982, 984, 985, 986, 987, 988, 989, 990, 991, 993, C15, C18, C19, C20, C22, C25, C34, C50, C56, C61, C82, C83, C85, C91, C92, C93, C94, C95, D00, D05, D010, D011, D012, D022, D075 OHIP: 203, 204, 205, 206,

		207, 208, 150, 154, 155, 157, 162, 174, 175, 183, 185
Chronic Liver Disease	CIHI DAD NACRS OHIP	ICD10: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 OHIP FEE: Z551, Z554 OHIP DX : 571, 573, 070
Ischemic Stroke	CIHI DAD NACRS	ICD10= H341, I630, I631, I632, I633, I634, I635, I638, I639, I64
Atrial Fibrillation/Flutter	CIHI DAD	ICD10:I48
Arrhythmia (not AF)	CIHI DAD NACRS OHIP	ICD10: I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000 R001 OHIP FEE: G178, G179, G249, G261, G259, Z443, Z431, Z437
Myocardial infarction	CIHI DAD NACRS	ICD-10: I21, I22
Congestive heart failure	CIHI DAD OHIP	ICD 10: I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 Canadian Classification of Health Interventions (CCI): 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP fee code: R701, R702, Z429 OHIP diagnosis code: 428
Coronary artery disease (excluding angina)	CIHI DAD NACRS OHIP	NACRS CCI: 1IJ76 CIHI-DAD ICD10-I21, I22, Z955, T822 OHIP FEE: R741, R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448 OHIP DX: 410, 412
Coronary artery Bypass Grafting (CABG)	CIHI DAD OHIP	CCI: 1IJ76 OHIP: R742, R743, E654, E645, E652, E646
Chronic Obstructive Pulmonary Disease (COPD)	CIHI DAD OHIP	A patient is said to have COPD if s/he had one physician claim COPD diagnosis in OHIP or one COPD hospitalization in CIHI-SDS or CIHI-DAD and is age 35 years or older
Percutaneous coronary intervention	CIHI-DAD OHIP	CCI: 1IJ50, 1IJ57GQ, 1IJ54GQAZ OHIP fee code: Z434, G262, G298

THESIS MANUSCRIPT I SUPPLEMENTAL TABLES 3-5

Supplemental Table 3. Crude and adjusted hazard ratios comparing immigrants versus non-immigrants for risk of incident chronic kidney disease re-defined as two outpatient eGFR measurements <60 mL/min/1.73m^2 at least 90 days apart.

Populations Compared	Crude HR (95% CI)	Adjusted HR (95% CI)
Immigrants vs. Non-Immigrants	0.39 (0.39-0.40)	0.78 (0.77-0.78)
Refugee Immigrants vs. Non-Refugee Immigrants	0.80 (0.78-0.82)	1.10 (1.07-1.12)

Abbreviations: HR, hazard ratio.

Supplemental Table 4.

Supplemental Table 4. Crude and adjusted hazard ratios comparing immigrants versus non-immigrants for risk of incident chronic kidney disease utilizing Fine-Gray subdistribution hazard models accounting for the competing risk of death.

Populations Compared	Crude HR (95% CI)	Adjusted HR (95% CI)
Immigrants vs. Non-Immigrants	0.45 (0.44-0.46)	0.83 (0.83-0.84)
Refugee Immigrants vs. Non-Refugee Immigrants	0.87 (0.85-0.88)	1.12 (1.10-1.14)

Abbreviations: HR, hazard ratio.

Supplemental Table 5.

Supplemental Table 5. Crude and adjusted hazard ratios comparing immigrants versus non-immigrants for risk of incident chronic kidney disease adjusting for urine ACR.

Populations Compared	Crude HR (95% CI)	Adjusted HR (95% CI)
Immigrants vs. Non-Immigrants	0.43 (0.43-0.44)	0.86 (0.82-0.89)
Refugee Immigrants vs. Non-Refugee Immigrants	0.87 (0.85-0.88)	1.10 (0.98-1.24)

Abbreviations: ACR, albumin-to-creatinine ratio; HR, hazard ratio.

MANUSCRIPT I FIGURES 2-3

Figure 2. Adjusted Cumulative Incidence Curves for Chronic Kidney Disease among Immigrants Versus Non-Immigrants.

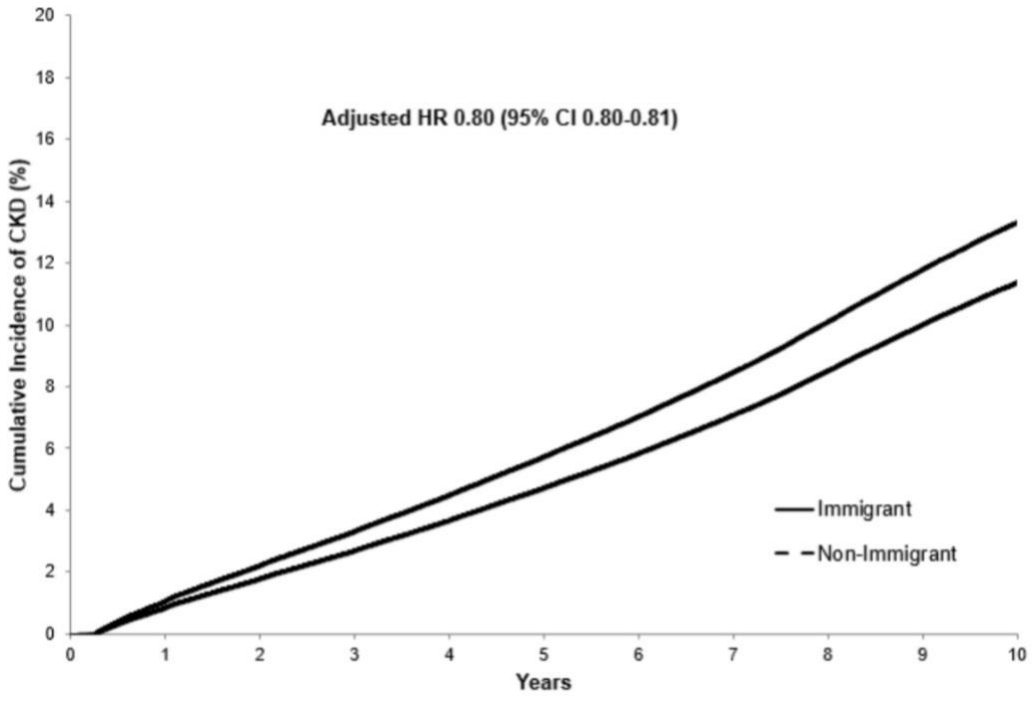


Figure 2

Chronic kidney disease defined as outpatient eGFR <60 mL/min/1.73m^2. Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery) determined at index.

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio.

Figure 3. Risk of Incident Chronic Kidney Disease among Immigrants by World Region of Origin.

World Region of Origin	Adjusted HR for Incident CKD (95% CI)	Forest Plot
Non-Immigrant	Reference	
North America	0.99 (0.97-1.01)	
Africa	0.97 (0.95-0.99)	
South America	0.90 (0.88-0.93)	
Middle East	0.89 (0.87-0.91)	
Europe	0.78 (0.77-0.80)	
Asia	0.73 (0.72-0.74)	

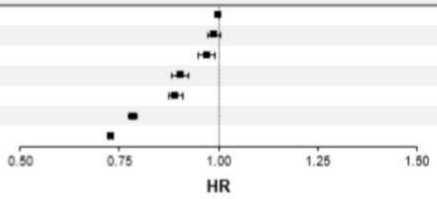


Figure 3

Chronic kidney disease defined as outpatient eGFR <60 mL/min/1.73m^2. Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

MANUSCRIPT II TABLES 3, S3-S5

Table 3. Outcome Events and Incidence Rates among Immigrants and Non-Immigrants

Table 3. Outcome Events and Incidence Rates among Immigrants and Non-Immigrants.

Outcome Event	Immigrants	Non-Immigrants
Composite Kidney Outcome		
Events, N (%)	46,168 (2.05)	369,892 (4.52)
Incidence Rate, Events/1,000 Person-Years (95% CI)	2.77 (2.75-2.80)	5.96 (5.94-5.98)
40% eGFR Decline		
Events, N (%)	46,008 (2.04)	368,173 (4.50)
Incidence Rate, Events/1,000 Person-Years (95% CI)	2.77 (2.74-2.79)	5.93 (5.91-5.95)
Kidney Failure		
Events, N (%)	1,912 (0.08)	10,970 (0.13)
Incidence Rate, Events/1,000 Person-Years (95% CI)	0.11 (0.11-0.12)	0.17 (0.17-0.18)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

MANUSCRIPT II SUPPLEMENTAL TABLE S3. - S5

Supplementary Table S3. Crude and Adjusted Hazard Ratios for Kidney Outcomes by Immigrant Status.

	HR for Immigrants vs. Non-Immigrants	
Outcome Event	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Composite Kidney Outcome	0.47 (0.46-0.47)	0.70 (0.69-0.71)
40% eGFR Decline	0.47 (0.46-0.47)	0.70 (0.69-0.71)
Kidney Failure	0.67 (0.64-0.71)	0.79 (0.75-0.83)

Abbreviations: HR, hazard ratio.

Supplementary Table S4. Crude and Adjusted Hazard Ratios for Kidney Outcomes among Refugee and Non-Refugee Immigrants.

Outcome Event	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Refugees vs. Non-Immigrants		
Composite Kidney Outcome	0.49 (0.48-0.50)	0.80 (0.79-0.82)
40% eGFR Decline	0.49 (0.48-0.50)	0.80 (0.79-0.82)
Kidney Failure	0.84 (0.76-0.93)	0.93 (0.84-1.03)
Non-Refugees vs. Non-Immigrants		
Composite Kidney Outcome	0.46 (0.46-0.46)	0.68 (0.67-0.69)
40% eGFR Decline	0.46 (0.46-0.47)	0.68 (0.66-0.69)
Kidney Failure	0.64 (0.61-0.67)	0.76 (0.72-0.81)
Refugees vs. Non-Refugees		
Composite Kidney Outcome	1.07 (1.04-1.09)	1.20 (1.17-1.23)
40% eGFR Decline	1.07 (1.04-1.09)	1.20 (1.17-1.23)
Kidney Failure	1.32 (1.18-1.47)	1.26 (1.13-1.42)

Abbreviations: HR, hazard ratio.

Supplementary Table S5. Crude and Adjusted Hazard Ratios for Kidney Outcomes among Immigrants with Recent (2005-2020) and Remote (1985-2004) Landing Dates.

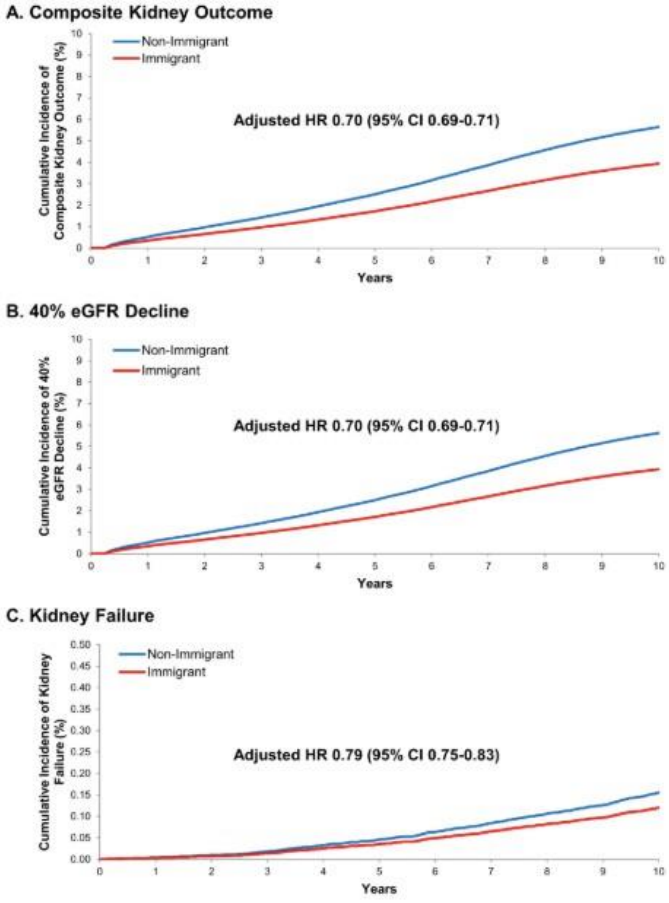
Outcome Event	Crude HR (95% CI)	Adjusted HR (95% CI)
Recent Immigrants vs. Non-Immigrants		
Composite Kidney Outcome	0.31 (0.31-0.32)	0.67 (0.66-0.68)
40% eGFR Decline	0.31 (0.31-0.32)	0.67 (0.66-0.68)
Kidney Failure	0.45 (0.41-0.50)	0.74 (0.67-0.82)
Remote Immigrants vs. Non-Immigrants		
Composite Kidney Outcome	0.54 (0.54-0.55)	0.71 (0.70-0.72)
40% eGFR Decline	0.54 (0.54-0.55)	0.71 (0.70-0.72)
Kidney Failure	0.77 (0.73-0.81)	0.81 (0.76-0.85)
Recent Immigrants vs. Remote Immigrants		
Composite Kidney Outcome	0.57 (0.56-0.59)	0.94 (0.92-0.96)
40% eGFR Decline	0.57 (0.56-0.59)	0.94 (0.92-0.96)
Kidney Failure	0.59 (0.52-0.66)	0.92 (0.82-1.03)

Abbreviations: HR, hazard ratio.

MANUSCRIPT II FIGURES CONTINUED

Manuscript II Figure 2. Adjusted Cumulative Incidence Curves for Adverse Kindy

Figure 2. Adjusted Cumulative Incidence Curves for Adverse Kidney Outcomes among Immigrants Versus Non-Immigrants.



Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery) determined at index.

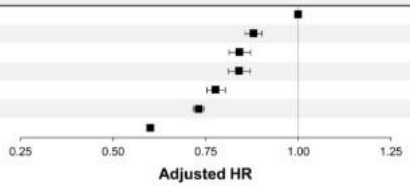
Abbreviations: CI, confidence interval; HR, hazard ratio.

Manuscript II Figure 3. Risk of Adverse Kidney Outcomes among Immigrants by World Region of Origin

Figure 3. Risk of Adverse Kidney Outcomes among Immigrants by World Region of Origin.

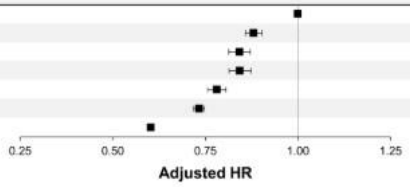
A. Composite Kidney Outcome

World Region of Origin	Adjusted HR (95% CI)
Non-Immigrant	Reference
North America	0.88 (0.86-0.90)
Africa	0.84 (0.81-0.87)
South America	0.84 (0.81-0.87)
Middle East	0.78 (0.75-0.80)
Europe	0.73 (0.72-0.75)
Asia	0.60 (0.59-0.61)



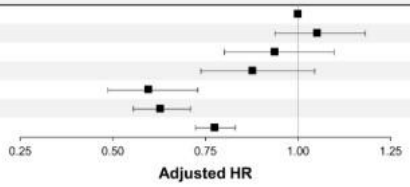
B. 40% eGFR Decline

World Region of Origin	Adjusted HR (95% CI)
Non-Immigrant	Reference
North America	0.88 (0.86-0.90)
Africa	0.84 (0.81-0.87)
South America	0.84 (0.81-0.87)
Middle East	0.78 (0.76-0.81)
Europe	0.73 (0.72-0.75)
Asia	0.60 (0.59-0.61)



C. Kidney Failure

World Region of Origin	Adjusted HR (95% CI)
Non-Immigrant	Reference
North America	1.05 (0.94-1.18)
Africa	0.94 (0.80-1.10)
South America	0.88 (0.74-1.05)
Middle East	0.60 (0.49-0.73)
Europe	0.63 (0.56-0.71)
Asia	0.78 (0.72-0.83)



Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighborhood income quintile, and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischemic stroke, congestive heart failure, and coronary artery bypass graft surgery).

Abbreviations: CI, confidence interval; HR, hazard ratio.