Trends in Cardiovascular-Kidney-Metabolic Risk Factors and Diseases and in Ontarian Adolescents and Young Adults, 2006-2023 – A Population-Based Cohort Study

Raidah Islam

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

Contributions

Raidah Islam is the primary author of all the contents presented in this thesis. Raidah Islam was responsible for: drafting the proposal, obtaining relevant data and completing the necessary privacy training to access said data, performing all statistical analyses using SAS, interpretation of results, creation of all tables and figure, and the writing, revision, and final submission of this thesis. Dr. Manish Sood is the senior author and supervised on all aspects of this project, including the overall study design. Dr. Sood along with Dr. Rahul Chanchlani and Dr. Daniel Myran formed the Thesis Advisory Committee (TAC) and provided valuable insight and suggestions for this project that were incorporated into this thesis. All members have approved of this thesis for submission. No patients or members of the public were involved in this project at any step.

This project was approved by the uOttawa office of ICES (formerly known as the Institute of Clinical Evaluative Sciences (ICES)) (TRIM = 2026 0901 486 000). Data from ICES was used to conduct this project and datasets were linked using unique encoded identifiers and were analyzed at ICES.

Funding and 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 study also received funding from: The Canadian Institutes of Health Research No. 198141 and The Heart and Stroke Foundation of Canada G-24-0038145. This document used data adapted from the Statistics Canada Postal CodeOM 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 CIHI, the Ontario Ministry of Health, and Toronto Community Health Profiles. 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. We acknowledge the Ontario Community Health Profiles Partnership as responsible for the sourcing of the Ontario Marginalization Index. We thank the Toronto Community Health Profiles Partnership for providing access to the Ontario Marginalization Index.

Raidah Islam would also like to acknowledge the Canadian Institutes of Health Research for awarding the Canada Graduate Scholarship – Master's (CGS-M) for a 12-month term (27, 000 CAD) during her time in the MSc Epidemiology program.

Ethics

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. All data is deidentified and can only be accessed remotely over a secure intranet platform by authorized personnel. The use of ICES data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA), as ICES is a prescribed entity under Ontario's privacy legislation. Section 45 authorizes ICES to collect and use health administrative data for analytical purposes

with respect to evaluating and monitoring the province's healthcare system. Thus, review by a research ethics board was not required for this thesis project.

The authors have no competing interests or conflicts of interest.

ABSTRACT

Background: Evidence suggests that the burden of cardio-kidney-metabolic (CKM) disease is shifting to younger populations. The objective of this thesis is to analyze recent trends in various CKM risk factors and disease outcomes in young Ontarians over the past two decades.

Methods: A retrospective population-based cohort study of Ontarians aged 13-40 years old was conducted using ICES data.

Results: Incidence of CKM outcomes such as diabetes, congestive heart failure, and arrythmia all significantly increased from 2006-2009 to 2020-2023 (IRRs 1.23-1.79, 95% CIs 1.17-1.93), while hyperlipidemia and coronary artery disease decreased (IRRs 0.54-0.75, 95% CIs 0.50-0.78). CKM trends also varied across different age strata, with 13-18 year olds seeing the largest annual percent increases in several critical outcomes.

Conclusions: Increases in key CKM risk factors and diseases have occurred in Ontario's younger population from 2006-2023. Future health strategies should focus on disease prevention in this population.

Word Count: 145/150

ACKNOWLEDGEMENTS

The journey of completing my Master's thesis in Epidemiology would not have been possible without all the support I've gotten over these last two years.

To my MSc thesis supervisor Dr. Manish Sood, thank you so much for your unwavering support throughout this whole process and for providing me with invaluable guidance from the first stages to the last. It has been an absolute pleasure working with you for the past two years and I hope to carry everything I learned with you in my future endeavors. I also want to thank Deena Fremont for all her support with my project and for answering any questions I had.

To my TAC members Dr. Rahul Chanchlani and Dr. Daniel Myran, thank you for your insightful feedback on this project which only strengthened my final work. I appreciate the clinical and methodological expertise you both brought to this project.

I would especially like to thank all the staff at ICES: Céline Girard, Vipuja Sivayogarajah**,** and Meltem Tuna for their immense help with getting me access to the data, training me on ICES procedures, cleaning data from ICES holdings, and for patiently answering all my questions and guiding me through the world of administrative data.

Finally, I would like to thank my family and friends for all their support and encouragement. In particular, I would like to thank Lisa, Ishika, and Gillian for being the greatest friends I could have found while being a student in the MSc Epidemiology program at uOttawa. Becoming the closest of friends throughout this journey has made all the struggle worthwhile and I cannot wait to start the next chapter of my life with you all by my side.

Table of Contents

PREFACE ii
Contributions ii
Funding and Acknowledgements ii
Ethics iii
ABSTRACT v
ACKNOWLEDGEMENTS vi
CHAPTER 1: Introduction 1
Background 1
Cardiovascular-Kidney-Metabolic Syndrome 1
Obesity and Other CKM Risk Factors on the Rise Amongst Younger People 2
The Burden of CVD and CKD Amongst Adolescents and Young Adults 3
Implications of Preventing CKM Diseases in Young People 4
Rationale 5
Research Question: 5
Objectives: 6
Structure of the Thesis 6
CHAPTER 2: Materials and Methods 7
Study Design 7
Data Sources 7
Study Population and Cohort Creation 9
Outcomes 9
Covariates and Variables of Interest 10
Statistical Analysis Plan 10
CHAPTER 3: Results 12
Participants 12
Table 1. Baseline Population Characteristics (Total Cohort and by Era of Entry) 13
Prevalence and Incidence of CKM Risk Factors and Diseases Across Time 15
Table 2. Total Period Prevalence and Number of New Cases by Era of Cardio-Kidney-Metabolic Outcomes Among Young People in Ontario, 2006–2023 17

Figure 1. Yearly (2006-2023) Age-Sex Standardized Incidence Rate of CKM Risk Factors 18

Figure 2. Yearly (2006-2023) Age-Sex Standardized Incidence Rate of CV Conditions ... 19

Figure 3. Yearly (2011-2023) Age-Sex Standardized Incidence Rate of CKD Indicators (ACR > 3 mg/mmol and 2 eGFRs < 60 mL/min/1.73 m^2) 20

Figure 4. Heatmap of Adjusted Incidence Rate Ratios by Era of CKM Risk Factors & Outcomes 21

Table 3. Adjusted Incidence Rate Ratios for Cardiovascular and Kidney Outcomes Across Eras Among Young People in Ontario 22

Age Group and Sex Differences in Temporal Trends of CKM Risk Factors and Diseases 23

Figure 5. Yearly (2006-2023) Crude Incidence Rates of CKM Risk Factors Stratified by Age Group 26

Figure 6. Yearly (2006-2023) Crude Incidence Rates of CKM Risk Factors Stratified by Sex 27

Figure 7. Yearly (2006-2023) Crude Incidence Rates of CV Conditions Stratified by Age Group 28

Figure 8. Yearly (2006-2023) Crude Incidence Rates of CV Conditions Stratified by Sex 29

Figure 9. Yearly (2006-2023) Crude Incidence Rates of CKD Indicators Stratified by Age Group 30

Figure 10. Yearly (2006-2023) Crude Incidence Rates of CKD Indicators Stratified by Sex 31

Figure 11. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKM Risk Factors 32

Figure 12. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CV Conditions 34

Figure 13. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKD Indicators 35

Table 4. Adjusted Incidence Rate Ratios for Cardiovascular Outcomes Among Young People in Ontario (2010-2014 v.s. 2006-2009) by Age Group and Sex 36

Table 5. Adjusted Incidence Rate Ratios for CKM Outcomes Among Young People in Ontario (2015-2019 v.s. 2006-2009/2011-2014*) by Age Group and Sex 37

Table 6. Adjusted Incidence Rate Ratios for CKM Outcomes Among Young People in Ontario (2020-2023 v.s. 2006-2009/2011-2014*) by Age Group and Sex 38

Table 7. Age Group x Era Interaction *p*-values 39

Figure 14. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKM Risk Factors 40

Figure 15. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CV Diseases 42

Figure 16. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKD Indicators 43

Table 8. Average Annual Percent Change in Incidence by Age Group, 2006–2023 44

CHAPTER 4: Discussion 45

Strengths and Limitations 48

Conclusion 49

References 51

Supplementary Materials 58

Table S1. ICES Databases Used and Accessed in this Study 58

Table S2: Data Definitions and Study Outcomes Across Datasets 60

Analysis of Obesity Trends 73

Table S3. Period Prevalence, New Cases per Era, and Adjusted Incidence Rate Ratios by Era for Obesity in Young People (13-40 years old) in Ontario 74

Table S4. Adjusted Incidence Rate Ratios (Era v.s. 2006-2009) by Age Group and Sex and Annual Percent Change in Incidence for Obesity Among Young People in Ontario 75

Figure S1. Results of the Analysis for Obesity in Young Ontarians (13-40 Years Old) 77

Additional CKD Analysis 78

Table S5. Adjusted[1] Incidence Rate Ratios (95% CI) by Era for CKD Indicators in Young People (13-40 years old) in Ontario 78

Table S6. Adjusted[1] IRRs (v.s. Reference Era 2011-2014) and APCs (95% CIs) by Age Group and Sex for CKD Indicators 79

Figure S2. Adjusted[1] Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKD Indicators 80

Figure S3. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKD Indicators 81

CHAPTER 1: Introduction

Background

Cardiovascular-Kidney-Metabolic Syndrome

Cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic conditions such as diabetes mellitus remain significant health challenges in Canada (1–3). Research has revealed there to be a strong interplay between metabolic risk factors, poor kidney health, and negative impacts on the cardiovascular system (4,5). Contributors to poor metabolic health include excess adiposity and impaired adipose tissue function, which in turn can lead to insulin resistance and inflammation, which untreated can result in the development of metabolic risk factors such as diabetes and hypertension (6,7). The presence of one or more of these metabolic conditions significantly heightens an individual's risk of developing CVD through damaging effects on vascular function (7,8). Similarly, poor kidney health is known to mediate the link between metabolic risk factors and CVD, including exacerbating the risk for heart failure (9). The well-documented existence of these significant interactions underscores the importance and need to consider all three facets of dysfunction in relation to each other. As a result, the American Heart Association recently defined this interconnected health disorder as cardiovascular-kidney-metabolic (CKM) syndrome (10). In a recent advisory report, the association proposes a staging model based on evidence regarding the highly progressive nature of CKM syndrome (10). The development of excess and/or dysfunctional adipose tissue can begin early due to various biological and environmental exposures, as well as unhealthy lifestyle habits (11). This then leads to the development of metabolic risk factors such as hyperlipidemia, hypertension, type 2 diabetes and even CKD (6). Complications from these commodities can then give rise to

subclinical myocardial and atherosclerosis, and then ultimately clinical CVDs (10). As a result of these pathophysiological interactions between multiple body systems, CKM syndrome leads to long lasting damage of critical organs and thus puts individuals at a significantly higher risk for the progression and development of kidney failure and CVD—the latter of which accounts for a significantly high proportion of the burden of premature death and disability (12,13).

There is a strong body of evidence demonstrating that the treatment and management of known CKM risk factors is effective in reducing future kidney disease, CVD, and even death (14–16). Early onset of CKM risk factors is associated with a higher risk of developing CKD, CVD and related events later in life (17,18). While the prevalence of CKM conditions is typically higher amongst middle-aged and older adults, preliminary data suggests CKM-related disease outcomes are occurring at a younger age; driven by shifting trends in related risk factors (13,18).

Obesity and Other CKM Risk Factors on the Rise Amongst Younger People

In 2009, the prevalence of obesity amongst adults in Canada stood at approximately 25% but as of 2023 has increased to 32.7% (19). Researchers have also concluded that there have been modest annual increases in the odds of obesity during the COVID-19 pandemic compared to pre-pandemic years, with class II and III obesity increasing at a greater rate compared to class I, highlighting that there may be a growing trend towards severe obesity in recent years (19). This recent rise in obesity has been of particular concern amongst younger individuals. New results from the Canadian Health Measures Survey (2022-2024) reveal that within age groups, the largest increase in obesity was seen amongst young adults (aged 18 to 39 years old), with prevalence increases by approximately eight percentage points for both males and females from 2016-2019 to 2022-2024 (20). Furthermore, amongst children and adolescents, approximately 1

in 3 were classified as being at risk for developing weight-related health challenges in adulthood (20).

As alluded to above, obesity can give rise to various other metabolic risk factors including diabetes, hyperlipidemia, and hypertension, and often times these risk factors can present together. In a study of youths aged 12 to 18 years old with diabetes, it was found that dyslipidemia (hypertriglyceridemia being most common form) was most prevalent amongst those with type 2 diabetes and those with dyslipidemia were more likely to be obese (21). The presence of these metabolic risk factors in young individuals can have serious implications for long-term health. A recent retrospective cohort study revealed that hypertensive children were at a significantly higher risk of experiencing stroke and congestive heart failure compared to their non-hypertensive counterparts (22). Regarding trends in these risk factors, a 2010 study out of Ontario found that the proportion of adolescents (aged 14 to 15 years old) with obesity, high cholesterol, and/or hypertension increased from 17% to 21% over a period of 4 years from 2004-2008 (23). Additionally, a more recent cross-sectional study from the United States found significant increases in diabetes along with obesity amongst young adults aged 20 to 44 years old (24). Results from these studies highlight the alarming rise of critical risk factors in younger individuals and how it may be contributing to the emergence of chronic disease seen in this age group.

The Burden of CVD and CKD Amongst Adolescents and Young Adults

CVD is one of the leading causes of death in Canada and carries an economic burden of over 20 billion dollars in healthcare costs every year (25,26). Although CVD is more prevalent amongst older patients and the overall incidence of CVD has steadily decreased over decades, data suggests that this decline does not extend to young adults—whose incidence has remained

unchanged or increased over the years (27,28). A comprehensive analysis into the global burden of CVD amongst young people revealed that the age-standardized prevalence rate (per 100 000 people) of CVD significantly increased from 1477.54 to 1645.32 from 1990 to 2019 (29). Furthermore, the study found that this prevalence rate was higher in women compared to men, whereas the mortality rate from CVD was higher in men—highlighting relevant sex differences (29). This suggests that the burden of CVD may be shifting to a younger demographic.

Similarly, CKD remains a significant health burden in Canada, affecting approximately 4 million Canadians (30,31). Along with CVD, the burden of CKD is also paralleled by the increasing burden of risk factors such as obesity, hypertension, and diabetes—with the latter being the leading cause of kidney failure in Canada (30,32). In relation to this, a statistical analysis of population health data from the United States discovered that the likelihood of death due to CKD had increased amongst young adults and that this was likely associated with the increase in CKD caused by diabetes (33). Moreover, results from the 2019 Global Burden of Disease study reveal that the global age-specific incidence rate (per 100,000 population) of early-onset CKD in adolescents and young adults increased from approximately 25 to 32 from 1990 to 2019, indicating a significant change in the burden of CKD amongst a younger population over the years. (34). In all, results from these studies underscore an increasing need to prioritize this demographic in CKM related research and interventions.

Implications of Preventing CKM Diseases in Young People

There is overwhelming evidence suggesting that addressing CKM risk factors at a younger age can work to prevent the development of its associated diseases in later adulthood. With the noted rises in key metabolic risk factors, CKD, and CVD amongst adolescents and young adults, the risk of morbidity and premature mortality is significantly increased as well as the associated

economic burden, which is expected to rapidly increase in the coming decades (35). Using nationally representative data, researchers at the American Heart Association projected that health care costs related to CVDs for young adults aged 22 to 44 years old would see a 261% increase by 2050 (35). Though this poses a significant public health challenge, there are also ample opportunities for prevention by targeting this population. While there are many suitable pharmacological interventions that can target the individual facets of CKM syndrome at its various stages, targeting lifestyle habits, such as physical activity, dietary intake, and tobacco use, early on can provide a more cost-effective and accessible solution, as these behaviours typically form in adolescence and continue into adulthood (36–38). By acknowledging and better understanding how CKM risk factors and disease affect younger individuals, actionable steps can be taken at the individual and at the policy level to prevent and mitigate potential disease burden, leading to an overall healthier population.

Rationale

Given the growing concern regarding the CKM health of young people, the prevention of CKM-related disease outcomes presents as a critical public health issue. The modifiable nature of many of the most common CKM risk factors allows for possible mitigation and thus prevention of future diseases if they are identified and addressed at a younger age, further highlighting the importance of continuing and advancing research in this area. To our knowledge, there has been no recent investigation into the epidemiological trends in CKM risk factors and disease outcomes in Canadian adolescents and young adults. Thus, an exploration in a Canadian context using population-level data is needed to determine if any significant shifts have occurred.

Research Question: What are the trends in CKM risk factors and disease outcomes for adolescents and young adults (aged 13 to 40 years old) in Ontario, Canada?

Objectives:

1. To determine trends in CKM risk factors and disease outcomes in adolescents and young adults (aged 13 to 40 years old) over the past 20 years.

Structure of the Thesis

This thesis manuscript was written using the thesis 'by articles' format following the guidelines outlined by the University of Ottawa. This thesis manuscript is broken down into four distinct chapters. Chapter 1 presented pertinent background information regarding CKM disease and its growing burden, including a look into what the literature says, as well as detailing the research question and objective of the thesis. Chapter 2 goes over the detailed methodology and analytical plan that was executed in order to complete the objectives of this thesis. Chapter 3 presents the findings of the thesis and goes into detail regarding the trends observed in CKM risk factors and disease outcome in the population of interest. Finally, Chapter 4 interprets and contextualizes these findings, going over what implications this research has for future health policy, as well as acknowledging limitations of the study before offering closing remarks.

CHAPTER 2: Materials and Methods

Study Design

An open retrospective population-based cohort study of adolescents and young adults from Ontario aged 13 to 40 years old was conducted using data from linked health administrative databases housed at ICES to describe the prevalence and incidence of CKM risk factors and disease outcomes across time, from 2006 to the most recent year with full available data (2023). 2006 was chosen as the starting year as diagnostic codes from the International Classification of Diseases (ICD-9 and ICD-10) became widely used from then. The reporting of all observational analyses for this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (39).

Data Sources

ICES data was used in this study to describe the cohort and outcomes of interest. 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. ICES data repositories include coded and linkable health records at the patient level for the Ontarian population eligible for universal health coverage and links data from various national and provincial health surveys and databases. As of today, the repository includes health service records for up to an estimated 13 million individuals (40). These datasets were linked using unique encoded identifiers and analyzed at ICES. Patient identifiers are replaced by unique numeric code to ensure confidentiality and anonymity. 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. Section 45 authorizes ICES to collect and use health administrative data for analytical purposes with respect to evaluating and monitoring the province's healthcare system.

The Registered Persons Database was used to obtain the baseline characteristics of all eligible individuals that will make up the cohorts. Health services data repositories were used to define outcomes of interest and collect information on existing comorbidities during a 2-year lookback period from index. Information on hospitalizations and medical procedures was collected using the Discharge Abstract Database. Relevant diagnostic information from emergency department visits and surgery procedures was captured from the National Ambulatory Care Reporting System (NACRS) and Same Day Surgery (SDS) Database. The Ontario Health Insurance Plan (OHIP) database was also used to collect information on healthcare encounters from rendered physician services. ICES-derived cohorts including the Ontario Hypertension and Ontario Diabetes Datasets were used to determine those with hypertension and diabetes. Information on relevant indicators of kidney disease (albuminuria, estimated glomerular filtration rate (eGFR)) was obtained from the Ontario Laboratories Information System (OLIS). Data from Census Area Profiles and postal codes were used to collect information on geographical and demographic measures that are predictors of interest in this study. More details can be found in the Supplementary Materials (**Table S1**).

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.

Study Population and Cohort Creation

All individuals in Ontario who were 13 to 40 years old were included and comprise the study population. Aside from the initial age exclusion, a 5-year look back period was implemented to identify individuals who had CKM risk factors and disease outcomes during this period, and they were subsequently excluded. This exclusion was implemented to maximize the possibility of building a true incident cohort. The study cohort was created from 2006 to 2023. All eligible individuals 13 to 40 years old were indexed in 2006 and each subsequent year newly eligible individuals were entered into the study. Each individual was be followed from their index date into the study (for the majority of the cohort this was when they became 13 years old) up until the point they either experience the outcome(s) of interest, death, turn 41 years old, or reach the end of the study period.

Outcomes

The outcomes of interest in this study were CKM risk factors and diseases. CKM risk factors primarily included hyperlipidemia, hypertension, diabetes mellitus, smoking, and obesity. CKM disease outcomes included indicators of kidney disease (albuminuria, reduced eGFR) and the following CVD outcomes: coronary artery disease (CAD), acute coronary syndrome (ACS), arrhythmia, congestive heart failure (CHF), ischemic stroke, and venous thromboembolism/pulmonary embolism (VTE/PE). For kidney-related outcomes, having an albumin-to-creatinine ratio (ACR) measure greater than 3 mg/mmol and/or having 2 eGFR measures less than 60 mL/min/1.73 m2 at least 90 days apart were indicators of CKD. All outcomes of interest were chosen apriori. Validated algorithms from ICES and/or codes from the

ICD-9, ICD-10, OHIP, and information from labs were used to identify these outcomes from documented healthcare encounters (See Supplementary Materials, **Table S2**). To note, ICD coding for obesity has been found to be limited in sensitivity, making their use to determine the true prevalence and incidence of this risk factor more difficult. Therefore analysis of obesity trends will be exploratory and can be found in the Supplementary Materials rather than in the main results section.

Covariates and Variables of Interest

Covariates and variables of interest were selected based on previous literature, clinical relevance, and availability within ICES. These include age, sex (defined as male or female), neighbourhood income quintile (designated 1 to 5), rural residence (yes or no), comorbidities (ex. malignancy, non-kidney solid organ transplant, congenital heart disease, cardiac surgery, chronic liver disease, sickle cell disease, lung disease) and healthcare encounters. Comorbidities of interest were used to describe the health status of participants prior to their entry into the study and were chosen based on their likelihood to be more common in younger populations and their biological relation to CKM health.

Statistical Analysis Plan

Baseline characteristics of the study population was calculated as means and standard deviations for continuous variables (ex. age) and counts and percentages for categorical characteristics. Total period prevalence was calculated, and crude incidence rates, age-sex standardized incidence rates (using the standard Canadian population as of 2021), and incidence rate ratios were calculated and described by era (2006-2009, 2010-2014, 2015-2019, and 2020-2023), sex, and age groups (13-18, 18-25, 25-30, 31-35 and 36-40 years old). Due to evidence of overdispersion, negative binomial regression models were used to calculate incidence rate ratios

(IRRs) and corresponding 95% confidence intervals (CIs) to examine changes over time. Overdispersion was formally assessed by looking at the ratio between Pearson Chi-Square residuals and degrees of freedom. Sex stratified models were also fit to determine trends within each sex. Furthermore, era and age strata interactions were tested to determine whether CKM trends differed across age groups. Models were adjusted for age, sex, rural residence, and income quintile. Only a very small subset of the cohort was missing data on rural residence and income quintile (< 0.4%). Average annual percent change and corresponding 95% CIs were calculated by exponentiating model coefficients to obtain IRRs then subtracting 1 and multiplying by 100. Additional analysis of CKD outcomes in which the total numbers of ACR/eGFR laboratory tests conducted per year was adjusted for was also conducted (See Supplementary Materials). All analyses were performed using SAS Enterprise Guide, version 8.3.

CHAPTER 3: Results

Participants

Baseline characteristics of participants are presented in **Table 1**. Following exclusions a total of 5,678,408 individuals aged 13-40 years old were included in the study cohort from 2006-2023. For kidney-related outcomes, only those who had at least one ACR measure (n = 405,313) and two eGFR measures after index (n = 1,754,205) were included in the analysis. For the overall cohort, the mean age of participants at index was 21.15 (SD: ± 9.27) years old and there were approximately an even number of male (50.84%) and female (49.16%) participants. The majority of participants lived in urban areas of Ontario (88.49%) and fell relatively evenly across each income quintile. The most prevalent comorbidity amongst the cohort was lung disease, with 7.65% of participants having had a form of lung disease in the past 2 years prior to their index. Malignancy was the second most prevalent comorbidity amongst the cohort (2.65%), whereas a history of cardiac surgery, non-kidney organ transplant, sickle cell disease, and/or chronic liver disease were not as common. For those with laboratory data available, baseline median ACR was 0.70 (IQR: 0.4-2.0) mg/mmol and the mean eGFR was 117.1 (SD: ± 16.0) mL/min/1.73 m^2.

Table 1. Baseline Population Characteristics (Total Cohort and by Era of Entry)

Characteristic	Total Cohort (n=5678408)	Era of Entry into Cohort			
		2006-2009 (n=3788556)	2010-2014 (n = 654793)	2015-2019 (n = 667502)	2020-2023 (n = 567557)
Age at index	21.15 ± 9.27	25.12 ± 8.93	13.26 ± 2.18	13.13 ± 1.55	13.21 ± 2.00
Sex					
Male	2886740 (50.84)	1920195 (50.68)	335184 (51.19)	341284 (51.13)	290077 (51.11)
Female	2791668 (49.16)	1868361 (49.32)	319609 (48.81)	326218 (48.87)	277480 (48.89)
Rural Residence					
Yes	653220 (11.51)	447890 (11.83)	76952 (11.76)	69907 (10.49)	58471 (10.32)
No	5021138 (88.49)	3339099 (88.17)	577342 (88.24)	596343 (89.51)	508354 (89.68)
Income Quintile					
1	1051354 (18.58)	741954 (19.66)	109685 (16.82)	107721 (16.18)	91994 (16.24)
2	1086909 (19.21)	755796 (20.03)	118887 (18.24)	115161 (17.29)	97065 (17.13)
3	1147869 (20.29)	767250 (20.33)	133198 (20.43)	132809 (19.94)	114612 (20.23)
4	1190296 (21.04)	771110 (20.44)	144998 (22.24)	147569 (22.16)	126619 (22.35)
5	1181256 (20.88)	737036 (19.53)	145201 (22.27)	162697 (24.43)	136322 (24.06)
Comorbidities					
Malignancy	148934 (2.62)	124628 (3.29)	4940 (0.75)	9391 (1.41)	9975 (1.76)
Cardiac surgery	287 (0.01)	195 (0.01)	27 (0.00)	40 (0.01)	25 (0.00)
Congenital heart disease	12156 (0.21)	5208 (0.14)	2056 (0.31)	2672 (0.40)	2220 (0.39)
Non-kidney organ transplant	389 (0.01)	252 (0.01)	46 (0.01)	50 (0.01)	41 (0.01)
Sickle cell disease	5108 (0.09)	3107 (0.08)	616 (0.09)	693 (0.10)	692 (0.12)
Chronic liver disease	35953 (0.63)	31839 (0.84)	1593 (0.24)	1359 (0.20)	1162 (0.20)
[a]Lung disease	434312 (7.65)	291825 (7.70)	57429 (8.77)	51530 (7.72)	33528 (5.91)
[b]ACR (mg/mmol) (Median (IQR))	0.70 (0.4-2.0) (n = 405313)	0.80 (0.4-2.0) (n = 298676)	0.70 (0.4-1.7) (n = 57276)	0.70 (0.4-1.7) (n = 37048)	0.80 (0.5-1.8) (n = 12313)

[b]eGFR (mL/min/1.73 m^2)	117.1 ± 16.0 (n = 1754205)	113.7 ± 14.9 (n = 1255198)	124.2 ± 15.3 (n = 264340)	126.4 ± 15.2 (n = 180484)	131.6 ± 14.1 (n = 54183)
Primary Care Visit					
Yes	1299382 (22.88)	1141874 (30.14)	58399 (8.92)	58062 (8.70)	41047 (7.23)
No	4379026 (77.12)	2646682 (69.86)	596394 (91.08)	609440 (91.30)	526510 (92.77)
Referral to a specialist					
Cardiologist	46625 (0.82)	12484 (0.33)	9634 (1.47)	15240 (2.28)	9267 (1.63)
[c]Endocrinologist	31219 (0.55)	-	8006 (1.22)	14316 (2.14)	8897 (1.57)
[c]Nephrologist	29370 (0.52)	-	7760 (1.19)	13482 (2.02)	8128 (1.43)

*Continuous variables reported as mean ± SD, categorical variables reported as n (%)

[a]Lung disease includes asthma.

[b]Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Baseline ACR and eGFR were calculated using the first measure following index from all individuals with available lab values.

[c]Data regarding endocrinologist and nephrologist visits were only available 2010 onwards.

Prevalence and Incidence of CKM Risk Factors and Diseases Across Time

From 2006-2023, the most prevalent CKM risk factors amongst Ontarians 13-40 years old were hypertension and hyperlipidemia with the total period prevalence standing at 4.36% and 5.40% respectively. Diabetes affected 1.3% of the cohort, while smoking was considerably less prevalent at 0.58%. The most common CV diseases present amongst the population was arrhythmia, followed by ACS and CAD, with the total prevalence being 4.44%, 1.76%, and 1.21% respectively for these conditions. For CKD indicators, 17.9% of individuals had an ACR over 3 mg/mmol and the prevalence of those who met the CKD definition based on two eGFR measures less than 60 mL/min/1.73 m^2 at least 90 days apart was 0.38% **(Table 2)**.

Different patterns in age-sex standardized incidence emerged over time with respect of CKM risk factors (**Figure 1**). The incidence of hypertension and diabetes remained relatively stable across the years but saw significant increases in 2020-2023 compared to 2006-2009 (IRR 1.09, 95% CI 1.03-1.15 and IRR 1.23, 95% CI 1.17-1.29 respectively). On the other hand, incidence rates of hyperlipidemia decreased over the study period. By 2015-2019, the incidence rate of hyperlipidemia was approximately half of what it was in 2006-2009 (IRR 0.47, 95% CI 0.44-0.50). Rates of smoking declined significantly by 2020–2023 (IRR 0.53, 95% CI 0.49–0.57) (**Table 3, Figure 4**).

Amongst CV conditions, age-sex standardized incidence rates CAD and ACS decreased progressively while rates of arrhythmia, CHF, ischemic stroke, and VTE/PE all increased significantly (**Figure 2**). In comparison to 2006-2009, CAD incidence was 25% lower (IRR 0.75, 95% CI 0.72-0.78 and ACS incidence was 26% lower (IRR 0.74, 95% CI 0.71-0.76) by 2020-

2023. By contrast, the incidence of arrhythmia and ischemic stroke steadily climbed from 2006-2009 across all eras, with the highest increase occurring in 2015-2019 for ischemic stroke (IRR 1.38, 95% CI 1.32-1.44) and in 2020-2023 for arrhythmia (IRR 1.46, 95% CI 1.42-1.49). Similarly, the incidence rates for VTE/PE remained consistently elevated in later eras. CHF demonstrated the largest relative increase from 2006-2009 to 2020-2023, with the rate climbing by 79% (IRR 1.79, 95% CI .65-1.93) (**Table 3, Figure 4**).

The age-sex standardized incidence rates of both CKD indicators increased significantly from 2011-2014 (**Figure 3**). The incidence rate of having an ACR level above 3 mg/mmol nearly doubled by 2020-2023 (IRR 1.98, 95% CI 1.80-2.17). Similarly, the incidence rate of having eGFRs levels below 60 min/mL/1.73 m^2 significantly increased by 75% by 2020-2023 (IRR 1.75, 95% CI 1.59-1.92) (**Table 3**, **Figure 4**).

Table 2. Total Period Prevalence and Number of New Cases by Era of Cardio-Kidney-Metabolic Outcomes Among Young People in Ontario, 2006–2023

Outcome	Total Period Prevalence, % (n)	New Cases per Era			
		2006-2009 (N)	2010-2014 (N)	2015-2019 (N)	2020-2023 (N)
Cardio-Kidney-Metabolic Risk Factors					
Hypertension	4.36 (247675)	53767	63510	68821	61577
Diabetes	1.34 (76230)	16364	18867	21021	19978
Hyperlipidemia	5.40 (306614)	106027	81452	60385	58750
Smoking	0.58 (32861)	7694	11283	9610	4274
Cardiovascular Diseases Outcomes					
CAD	1.21 (68986)	16805	21028	17835	13318
ACS	1.76 (99761)	24532	30454	26014	18761
Arrhythmia	4.44 (251919)	46254	65102	71481	69082
CHF	0.16 (9234)	1460	2308	2691	2775
Ischemic Stroke	0.33 (18751)	3389	4998	5884	4480
VTE/PE	0.90 (50848)	8003	15087	16270	11488
Chronic Kidney Disease Outcomes*					
CKD: ACR > 3	17.9 (72505)	-	16831	27364	28310
[a]CKD: eGFR < 60	0.38 (6673)	-	1255	2773	2645

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Period prevalence and incidence for CKD indicators are restricted to those who had available OLIS data for ACR/eGFR. Thus, the column 2010-2014 should be interpreted as 2011-2014 for these outcomes.

[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

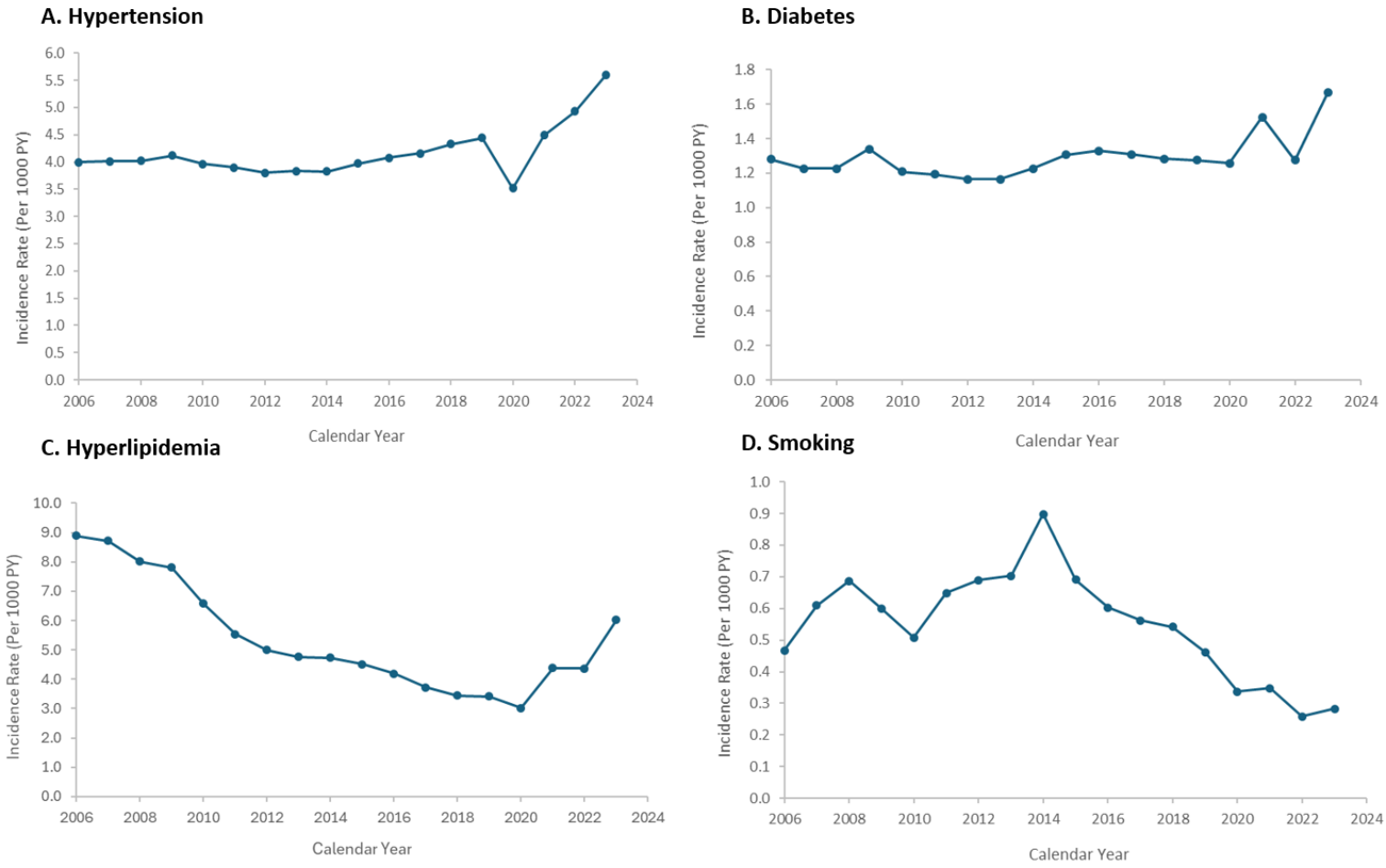


Figure 1. Yearly (2006-2023) Age-Sex Standardized Incidence Rate of CKM Risk Factors

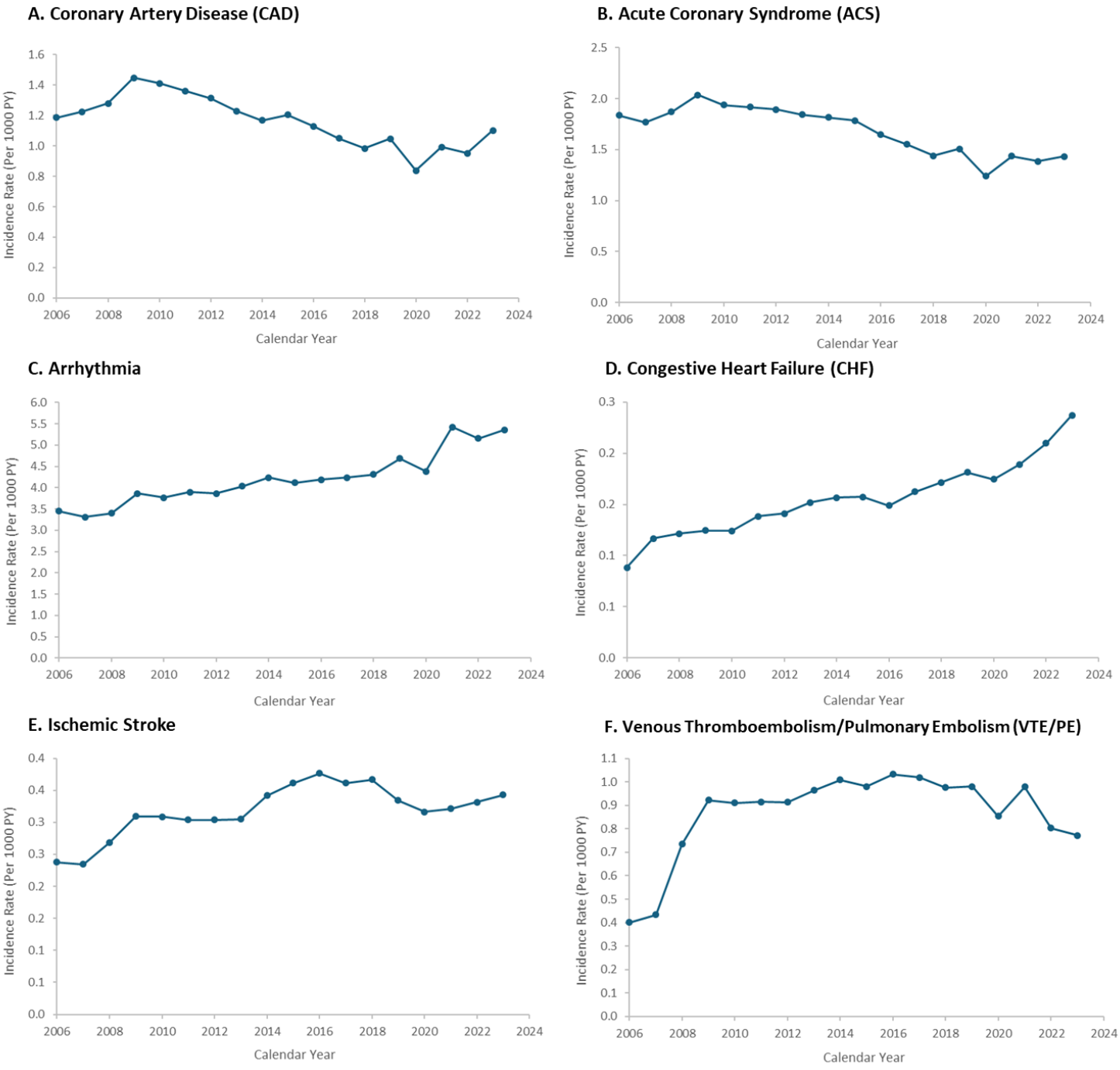
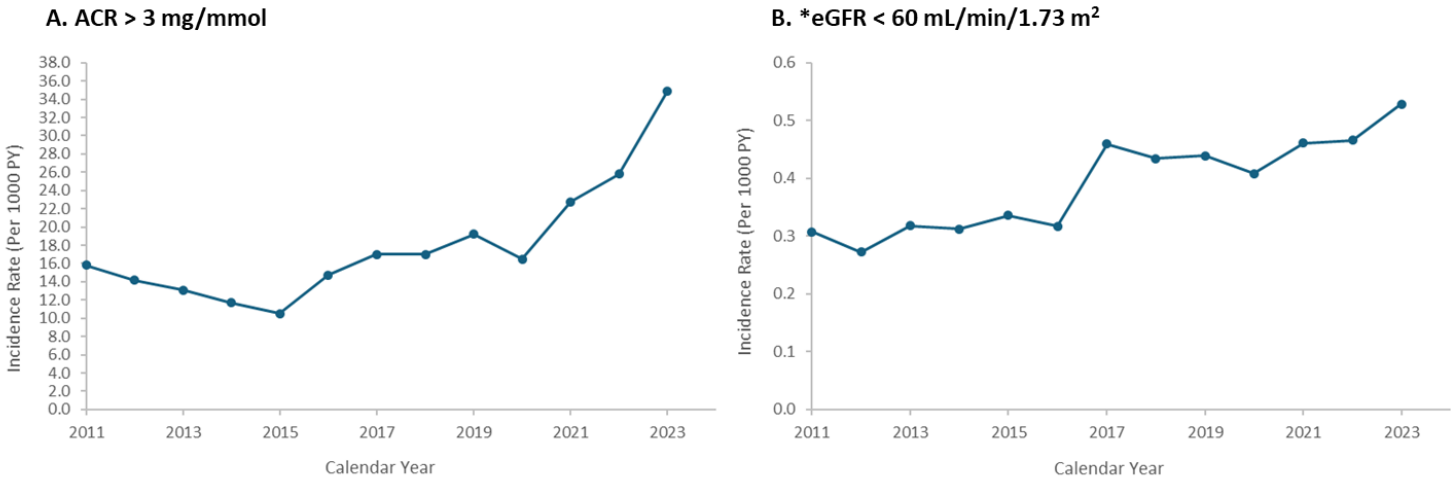
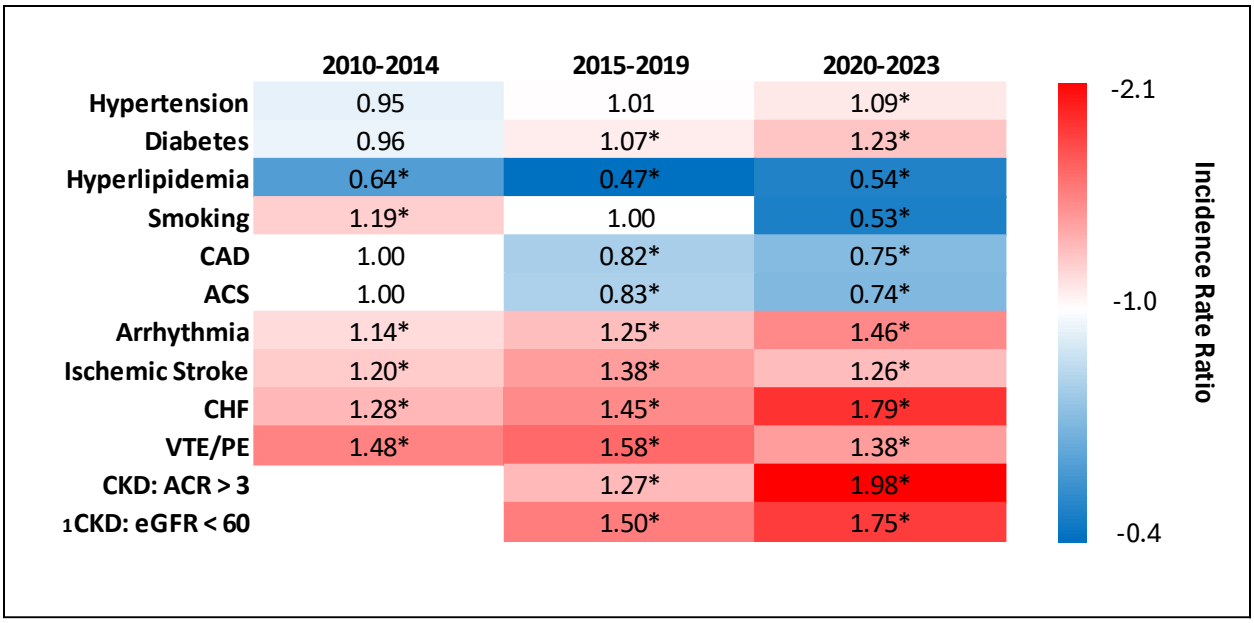


Figure 2. Yearly (2006-2023) Age-Sex Standardized Incidence Rate of CV Conditions



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 3. Yearly (2011-2023) Age-Sex Standardized Incidence Rate of CKD Indicators (ACR > 3 mg/mmol and 2 eGFRs < 60 mL/min/1.73 m^2)



*Indicates significance ($p < 0.05$). Models were adjusted for age, sex, rural residence, and income quintile.
[1]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 4. Heatmap of Adjusted Incidence Rate Ratios by Era of CKM Risk Factors & Outcomes

Table 3. Adjusted Incidence Rate Ratios for Cardiovascular and Kidney Outcomes Across Eras Among Young People in Ontario

	Era (v.s. 2006-2009/2011-2014*)		
Outcome	**2010-2014 IRR (95% CI)**	**2015-2019 IRR (95% CI)**	**2020-2023 IRR (95% CI)**
Cardio-Kidney-Metabolic Risk Factors			
Hypertension	0.95 (0.90-1.00)	1.01 (0.96-1.06)	1.09 (1.03-1.15)
Diabetes	0.96 (0.91-1.01)	1.07 (1.02-1.13)	1.23 (1.17-1.29)
Hyperlipidemia	0.64 (0.60-0.68)	0.47 (0.44-0.50)	0.54 (0.50-0.57)
Smoking	1.19 (1.11-1.27)	1.00 (0.94-1.08)	0.53 (0.49-0.57)
Cardiovascular Disease Outcomes			
CAD	1.00 (0.96-1.04)	0.82 (0.79-0.86)	0.75 (0.72-0.78)
ACS	1.00 (0.97-1.04)	0.83 (0.80-0.87)	0.74 (0.71-0.76)
Arrhythmia	1.14 (1.12-1.17)	1.25 (1.22-1.28)	1.46 (1.42-1.49)
CHF	1.28 (1.18-1.38)	1.45 (1.34-1.57)	1.79 (1.65-1.93)
Ischemic Stroke	1.20 (1.15-1.25)	1.38 (1.32-1.44)	1.26 (1.21-1.32)
VTE/PE	1.48 (1.41-1.56)	1.58 (1.51-1.66)	1.38 (1.31-1.45)
Chronic Kidney Disease Outcomes*			
CKD: ACR > 3	-	1.27 (1.16-1.40)	1.98 (1.80-2.17)
[a] CKD: eGFR < 60	-	1.50 (1.36-1.64)	1.75 (1.59-1.92)

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Thus, 2011-2014 is the reference period for kidney disease outcomes. Models were adjusted for age, sex, rural residence, and income quintile.
[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Age Group and Sex Differences in Temporal Trends of CKM Risk Factors and Diseases

Age-stratified analysis demonstrated several differences in temporal trends of CKM risk factors. While crude incidence rates were generally higher amongst older age groups (**Figure 5**), significant increases in hypertension and diabetes over time occurred amongst younger age groups. Compared to 2006-2009, incidence rates of diabetes rose substantially in 2015-2019 (IRR 1.53, 95% CI 1.36-1.72) and 2020-2023 (IRR 1.58, 95% CI 1.41-1.78) for those 13-18 years old, while the incidence of hypertension increased most prominently in those aged 25-30 years old (2020-2023: IRR 1.67, 95% CI 1.58-1.77) (**Tables 5-6, Figure 11**). Alternatively, incidence of hyperlipidemia saw modest declines in each age group across eras (**Tables 4-6, Figure 11)**. These trends are also reflected in the average annual percent change in incidence, with the largest increase for hypertension and diabetes seen for 25-30 (APC 4.7%, 95% CI 4.3-5.1%) and 13-18 year olds (APC 3.5%, 95% CI 3.0-4.0%) and respectively. The largest decrease across the study period for hyperlipidemia was seen in 31-35 year olds (APC -5.2%, 95% CI -5.7 to -4.7%) (**Table 8, Figure 14**). Overall, differing temporal trends across age groups were indicative for hypertension, diabetes, and hyperlipidemia (interaction p-values < 0.05; **Table 7**), although this was not evident for smoking (interaction $p = 0.13$).

Sex stratified analysis of CKM risk factors revealed that crude incidence rates of hypertension and hyperlipidemia tended to be higher within males, while rates of smoking were overall higher amongst females (**Figure 6**). However, temporal variation of incidence remained similar within each sex strata for most CKM risk factors, with some notable differences including diabetes incidence increasing by a higher proportion by 2020-2023 in females (IRR 1.29, 95% CI 1.21-1.37) (**Tables 4-6**).

For CV diseases, age-stratified crude incidence results show that oldest age groups had higher incidence rates overall for most of these conditions, though 19-30 year olds had higher incidence of arrhythmia compared to 36-40 year olds throughout the study period (**Figure 7**). However, direction of temporal trends varied by outcome. The incidence of CAD and ACS declined consistently across age groups, with the largest reduction occurring in 13-18 year olds by 2020-2023 (CAD IRR: 0.64, 95% CI 0.58-0.70; ACS IRR: 0.68, 95% CI 0.62-0.74) (**Table 6, Figure 12**). Contrastly, incidence rates of arrhythmia, CHF, ischemic stroke, and VTE/PE all demonstrated increases over time across most age groups. For instance, by 2020-2023, 19-24 year olds demonstrated a 58% increased incidence rate of arrhythmia (compared to 2006-2009) (IRR 1.58, 95% CI 1.51-1.66), whereas 19-40 year olds showed larger increases in CHF (IRRs 1.79-1.92, 95% CIs 1.51-2.22). Average annual percent change in incidence also demonstrate that increases in CHF throughout the study period was more common amongst young adults compared to adolescents (APCs 4.5-4.8%, 95% CIs 3.7-5.6%). Older age groups also had higher increases per year in VTE/PE compared to younger ones (APCs 2.8-2.9%, 95% CIs 2.2-3.5%) (**Table 8, Figure 15**). Age group-era interactions were significant for CAD, ACS, arrhythmia, CHF, and VTE/PE (interaction p-values < 0.05; **Table 7**), indicating that there was a significant difference in temporal trends between different age groups for these outcomes. No significant difference in era trends between age groups was shown for ischemic stroke (interaction $p = 0.16$).

Sex stratified analyses of CV diseases revealed males to have higher crude incidence rates of CAD and ACS compared to females, whereas females had higher rates of arrhythmia, ischemic stroke, and VTE/PE (**Figure 8**). There were similar increases across the years within both males and females for CAD and ACS. Within females, there was a 54% increase (IRR 1.54, 95% CI

1.50-1.58) in incidence rate for arrhythmia in 2020-2023 compared to a 37% (IRR 1.37, 95% CI 1.33-1.40) increase in males. Males had a 95% increase in CHF incidence by 2020-2023 (IRR 1.95, 95% CI 1.78-2.14) whereas females had a 66% increase (IRR 1.66, 95% CI 1.52-1.82) (**Table 6**).

With respect to CKD indicators, while crude incidence rates of both elevated ACR levels and reduced eGFR levels were higher overall in 31-40 year olds for most of the study period (**Figure 9**), distinct temporal trends are seen across age groups (interaction *p*-values for both outcomes < 0.0001; **Table 7**). The largest relative increases across eras were seen in the youngest age group. By 2020-2023, 13-18 year olds had an approximately four-fold increase in incidence of ACR > 3 mg/mmol (IRR 4.34, 95% CI 3.90-4.83) and eGFR < 60 min/mL/1.73 m^2 (IRR 4.09, 95% CI 3.04-5.49) compared to in 2011-2014 (**Table 6, Figure 13**). To add, there was an approximate 18% average annual increase in both elevated ACR and reduced eGFR levels for 13-18 year olds (**Table 8, Figure 16**). On the other hand, 36-40 year olds saw declines in the incidence of elevated ACR and reduced eGFR levels across time (**Table 5-6, Figure 13**).

Sex stratified analyses of increased ACR and decreased eGFR levels show an increase in incidence rates in both sexes. Females had a higher crude incidence of elevated ACR overall, whereas males had a higher crude incidence of reduced eGFR overall (**Figure 10**). Compared to the earliest era, in 2020-2023 there was a 220% increase (IRR 2.20, 95% CI 1.95-2.49) in incidence of elevated ACR within females and an 83% increase (IRR 2.20, 95% CI 1.95-2.49) in the incidence rate of having reduced eGFR in males (IRR 1.83, 95% CI 1.59-2.11) (**Table 6**).

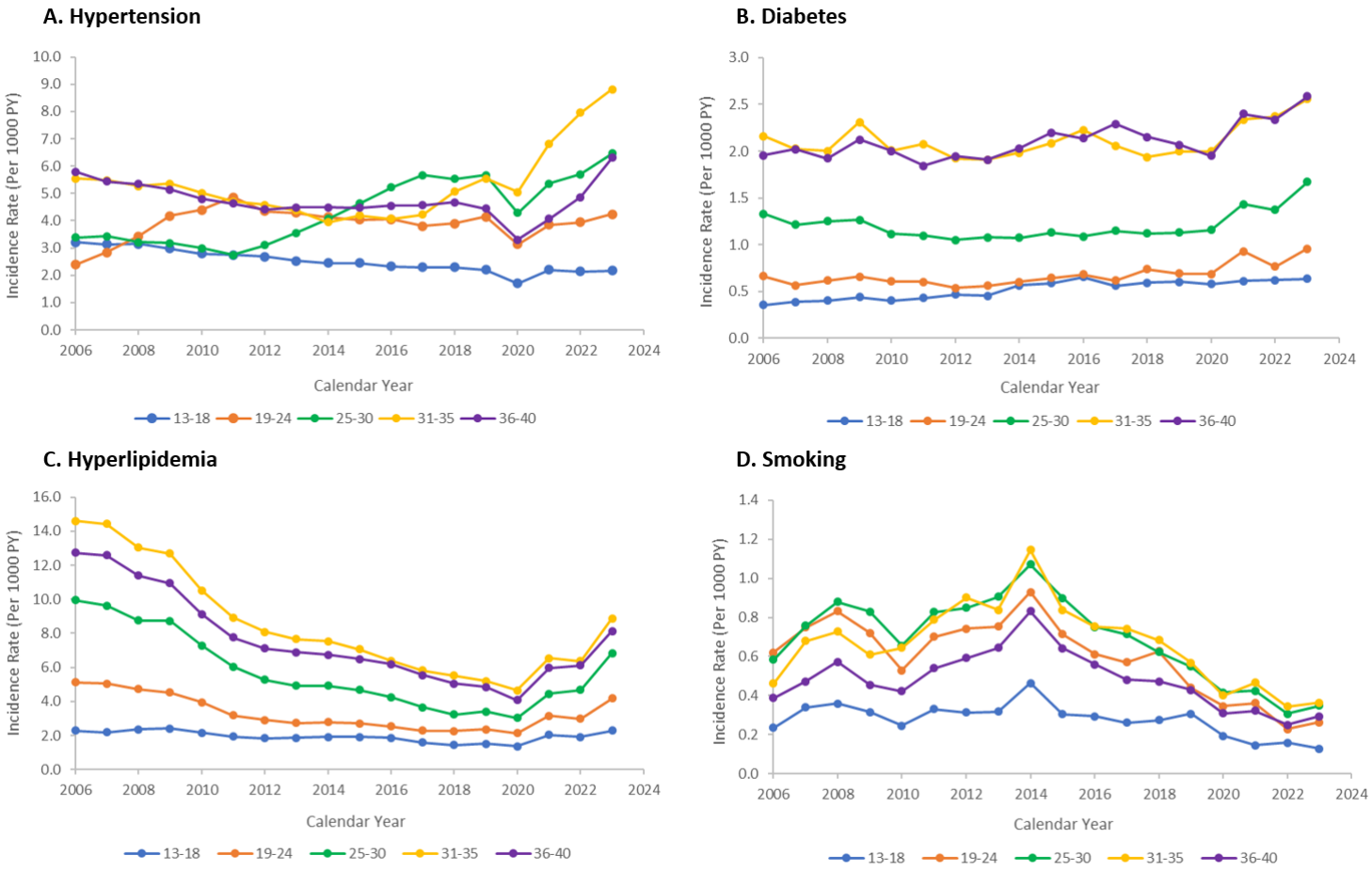


Figure 5. Yearly (2006-2023) Crude Incidence Rates of CKM Risk Factors Stratified by Age Group

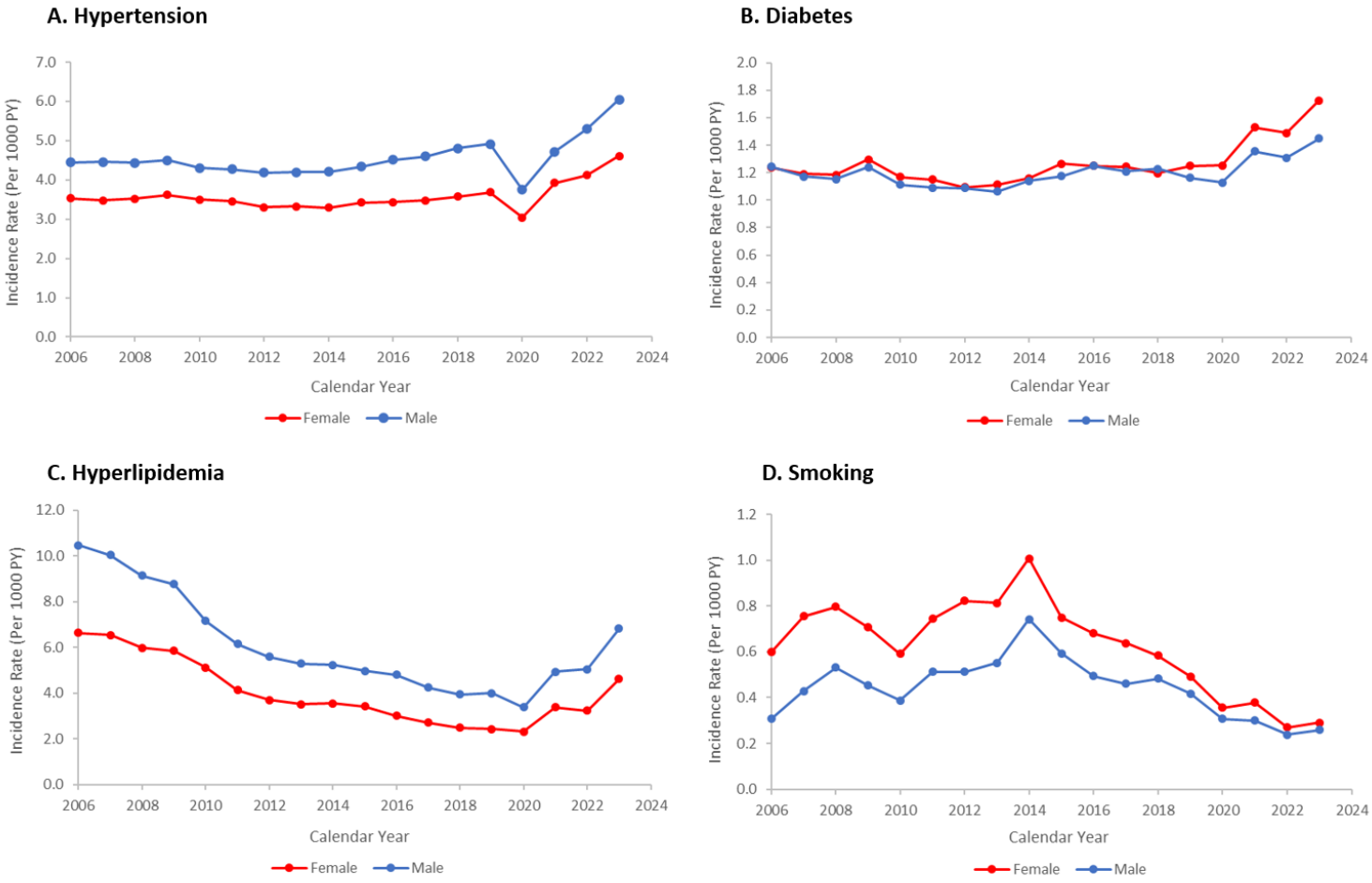


Figure 6. Yearly (2006-2023) Crude Incidence Rates of CKM Risk Factors Stratified by Sex

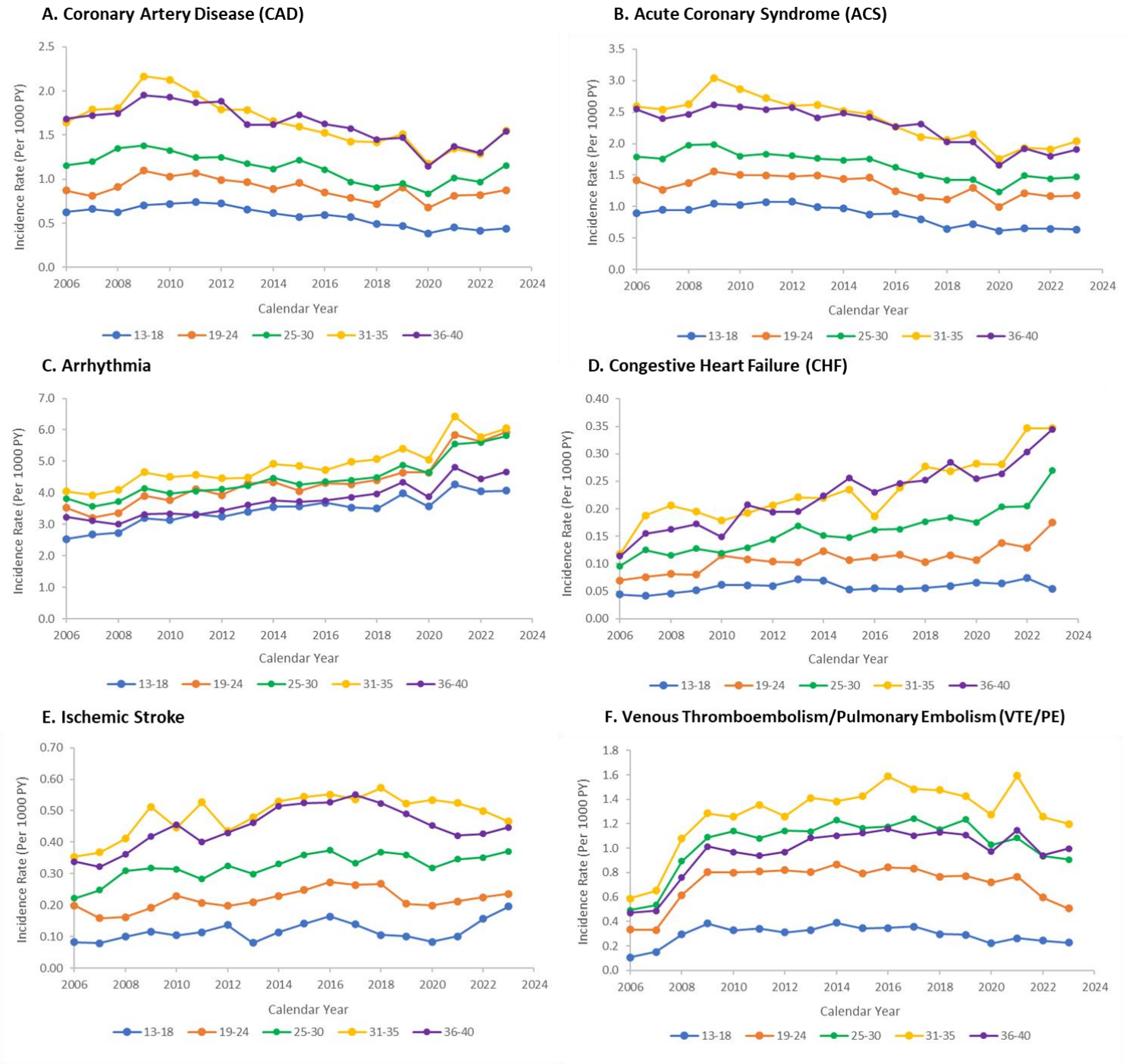


Figure 7. Yearly (2006-2023) Crude Incidence Rates of CV Conditions Stratified by Age Group

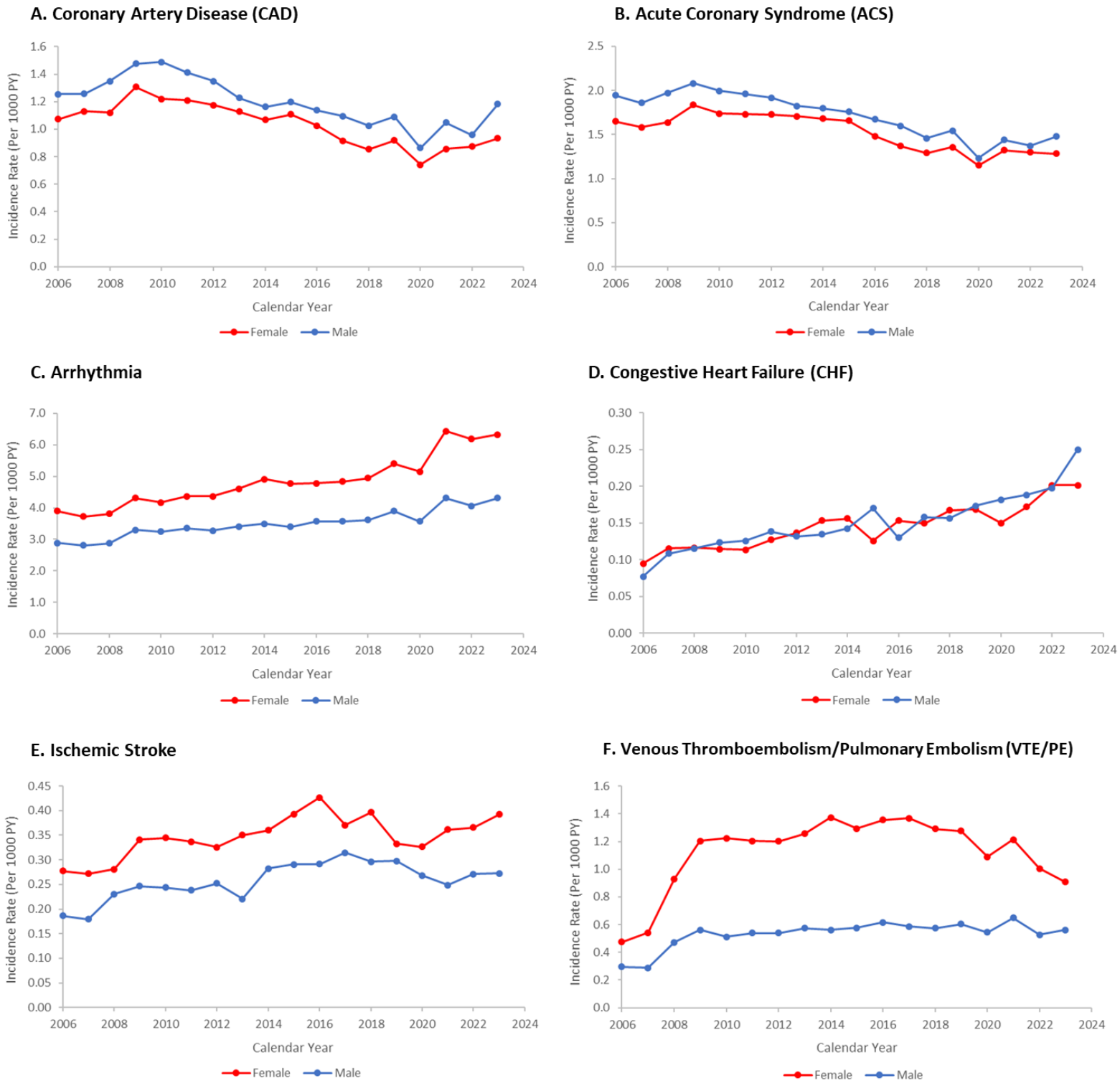
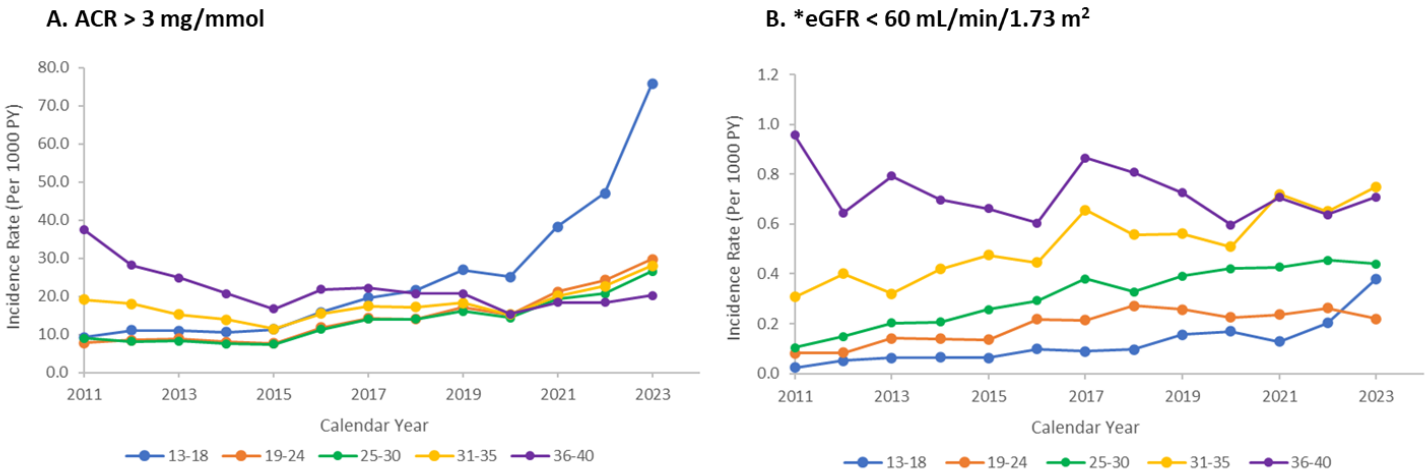
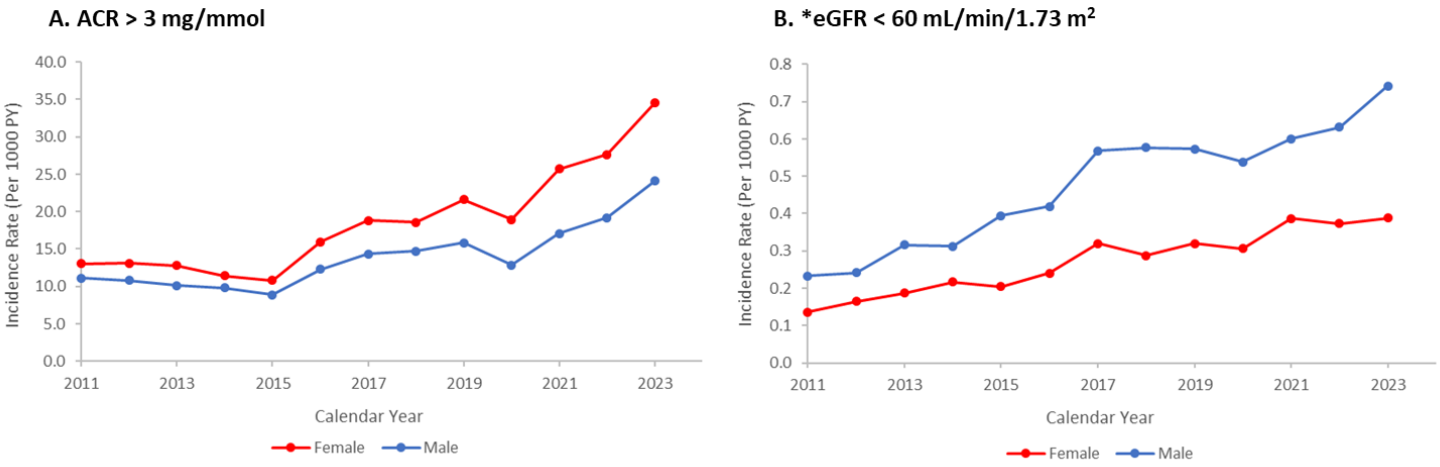


Figure 8. Yearly (2006-2023) Crude Incidence Rates of CV Conditions Stratified by Sex



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 9. Yearly (2006-2023) Crude Incidence Rates of CKD Indicators Stratified by Age Group



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 10. Yearly (2006-2023) Crude Incidence Rates of CKD Indicators Stratified by Sex

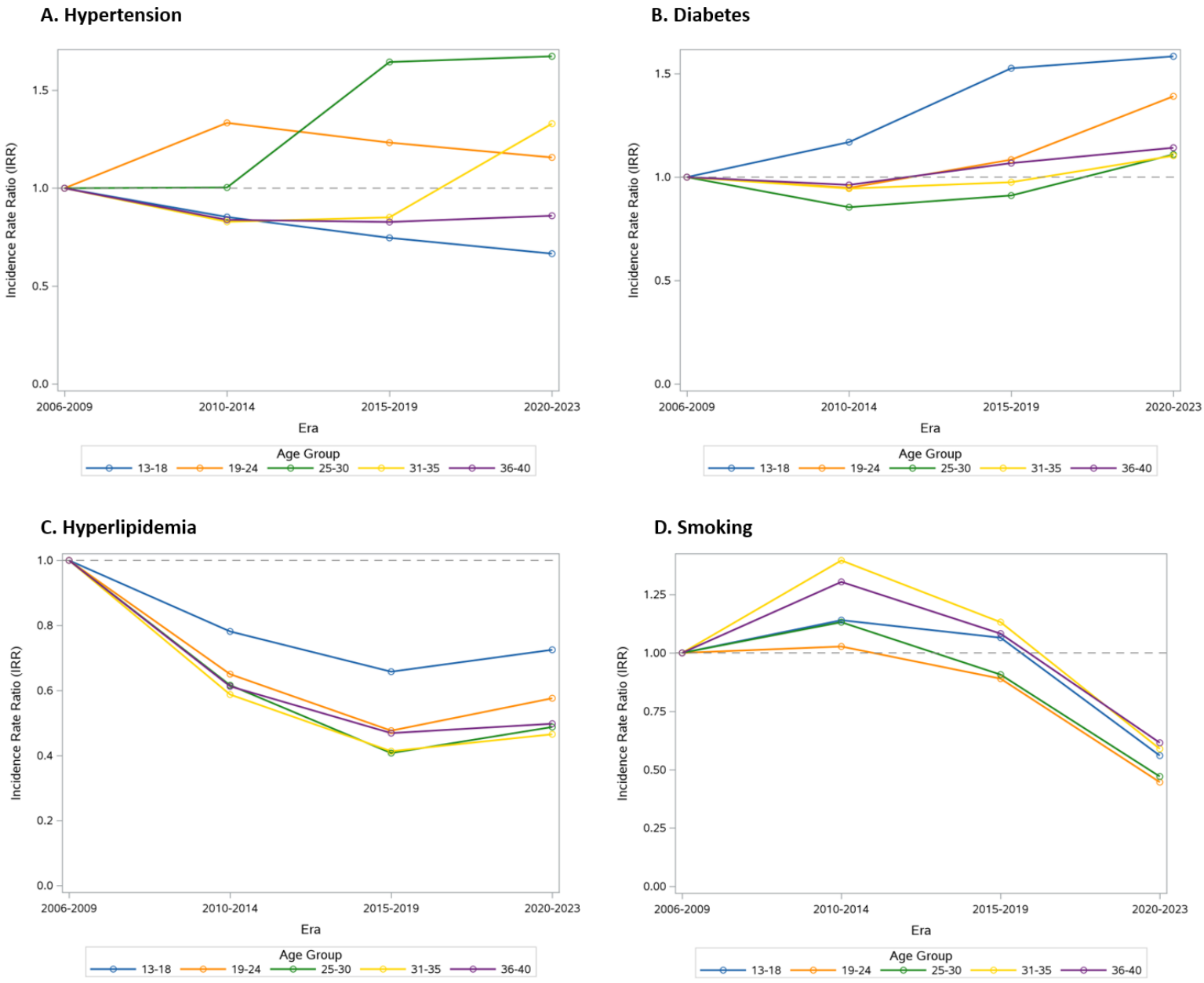
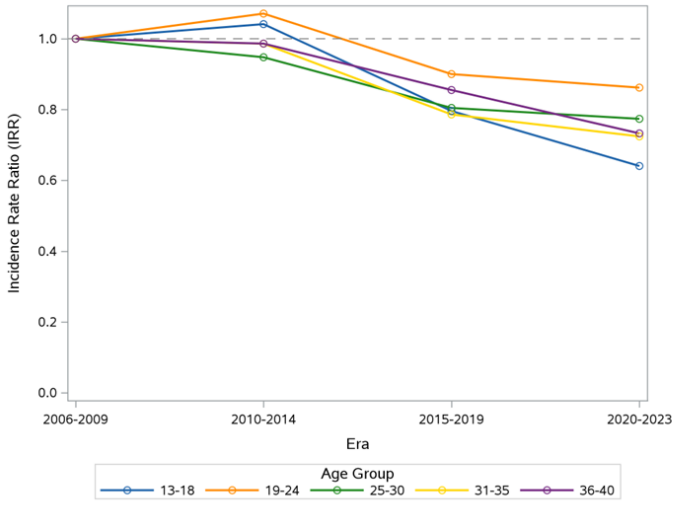
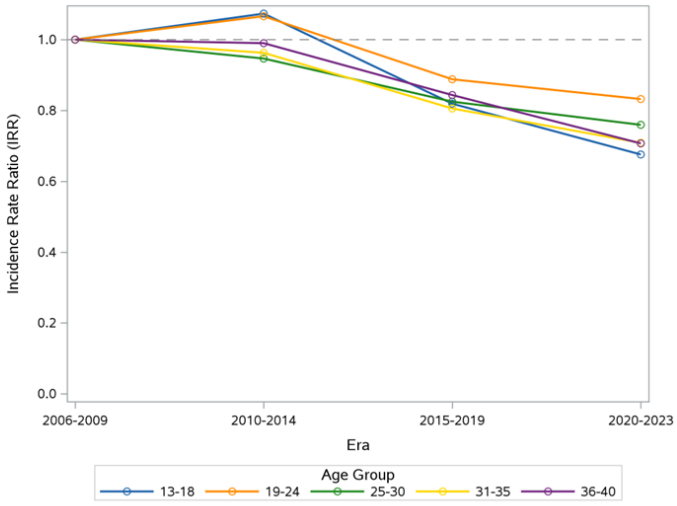


Figure 11. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKM Risk Factors

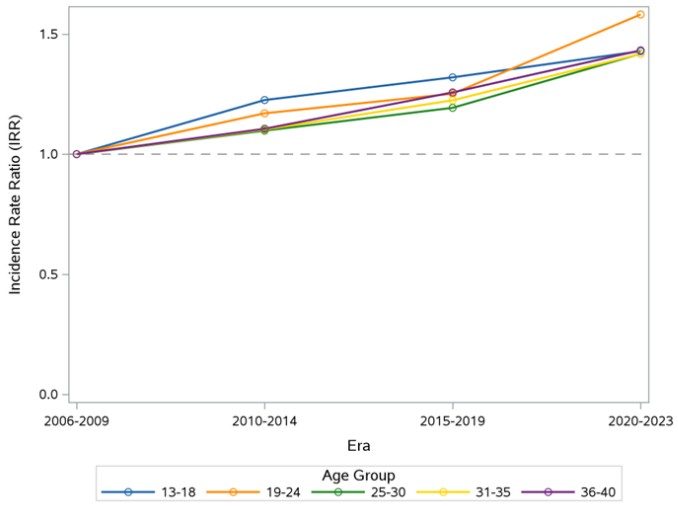
A. Coronary Artery Disease (CAD)



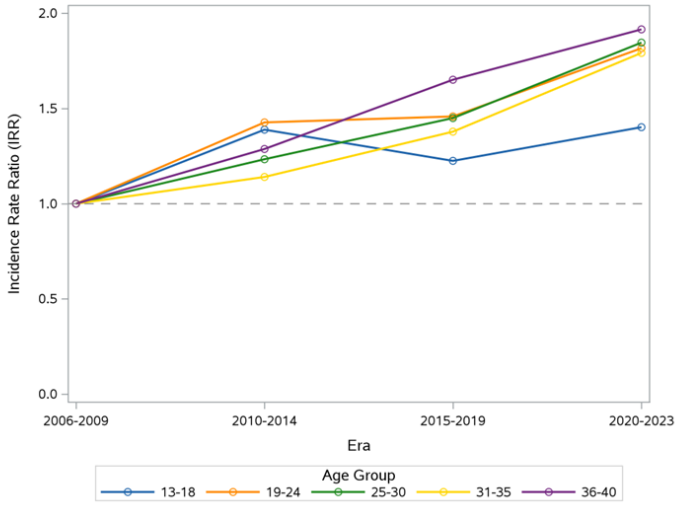
B. Acute Coronary Syndrome (ACS)



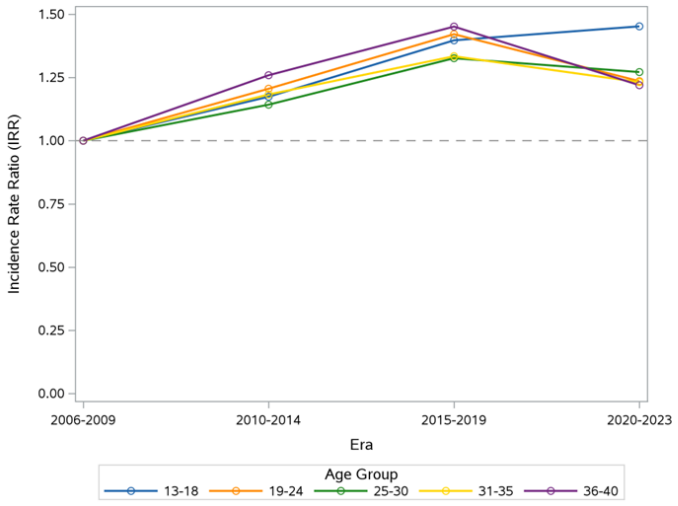
C. Arrhythmia



D. Congestive Heart Failure (CHF)



E. Ischemic Stroke



F. Venous Thromboembolism/Pulmonary Embolism (VTE/PE)

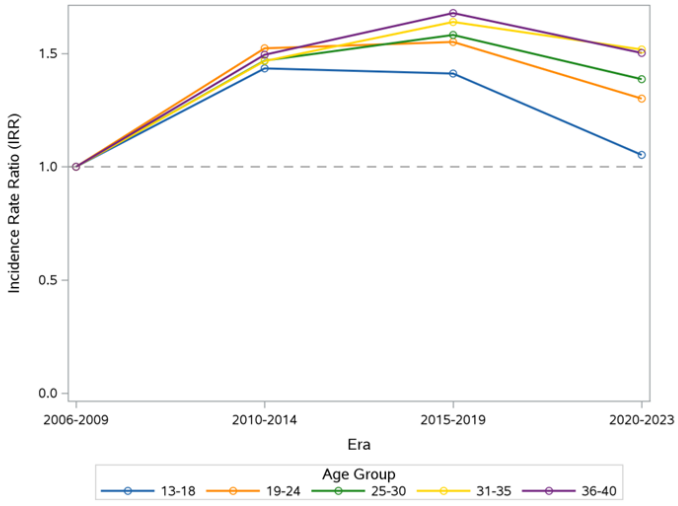
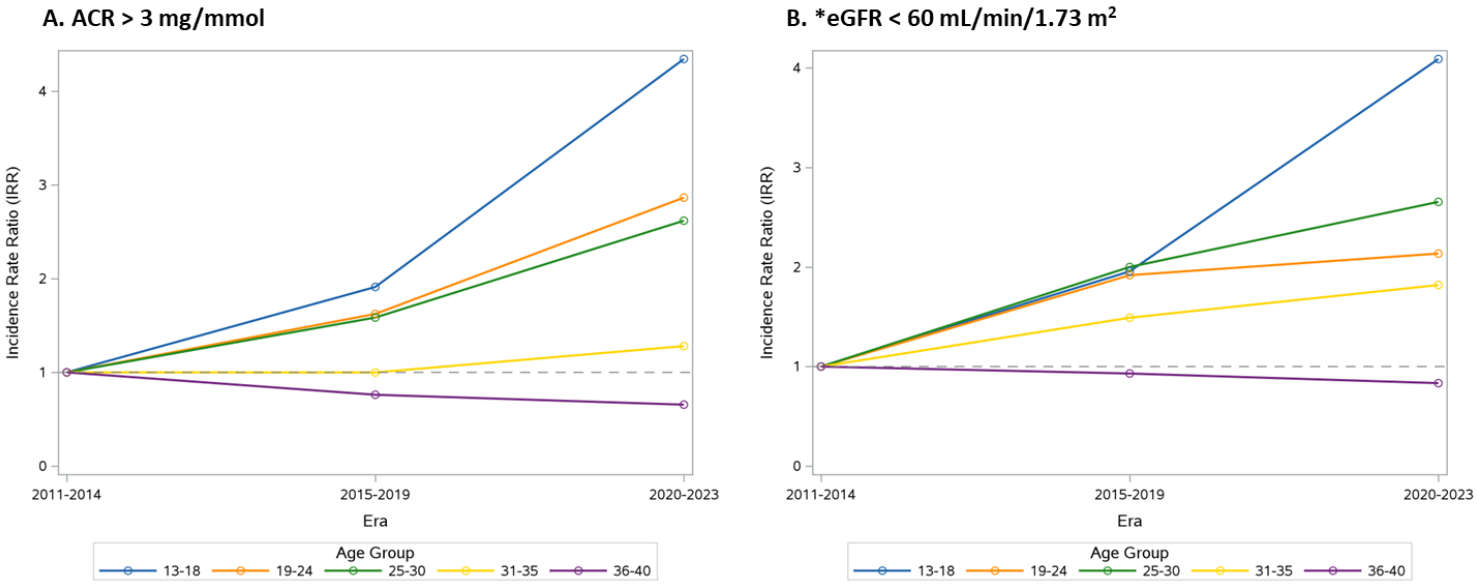


Figure 12. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CV Conditions



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 13. Adjusted Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKD Indicators

Table 4. Adjusted Incidence Rate Ratios for Cardiovascular Outcomes Among Young People in Ontario (2010-2014 v.s. 2006-2009) by Age Group and Sex

Outcome	Age Group					Sex	
	13-18 IRR (95% CI)	19-25 IRR (95% CI)	25-30 IRR (95% CI)	31-35 IRR (95% CI)	36-40 IRR (95% CI)	Male IRR (95% CI)	Female IRR (95% CI)
Cardio-Kidney-Metabolic Risk Factors							
Hypertension	0.85 (0.81-0.90)	1.33 (1.26-1.14)	1.00 (0.95-1.06)	0.83 (0.78-0.88)	0.84 (0.79-0.89)	0.95 (0.89-1.02)	0.94 (0.88-1.02)
Diabetes	1.17 (1.03-1.31)	0.95 (0.85-1.06)	0.85 (0.77-0.95)	0.94 (0.86-1.04)	0.96 (0.87-1.06)	0.96 (0.90-1.02)	0.96 (0.90-1.01)
Hyperlipidemia	0.78 (0.68-0.89)	0.65 (0.57-0.74)	0.62 (0.54-0.70)	0.59 (0.52-0.67)	0.61 (0.54-0.70)	0.64 (0.60-0.69)	0.64 (0.61-0.68)
Smoking	1.14 (0.97-0.34)	1.03 (0.89-1.19)	1.13 (0.98-1.31)	1.40 (1.20-1.63)	1.30 (1.11-1.53)	1.26 (1.17-1.36)	1.13 (1.03-1.23)
Cardiovascular Diseases							
CAD	1.04 (0.96-1.13)	1.07 (0.99-1.16)	0.95 (0.88-1.03)	0.99 (0.91-1.06)	0.99 (0.91-1.06)	1.00 (0.96-1.05)	1.01 (0.98-1.05)
ACS	1.07 (0.99-1.16)	1.06 (0.99-1.15)	0.95 (0.88-1.02)	0.96 (0.89-1.04)	0.99 (0.92-1.07)	0.98 (0.95-1.02)	1.03 (1.00-1.07)
Arrhythmia	1.23 (1.17-1.29)	1.17 (1.12-1.23)	1.10 (1.05-1.15)	1.10 (1.05-1.16)	1.11 (1.05-1.16)	1.13 (1.10-1.16)	1.15 (1.12-1.18)
CHF	1.39 (1.12-1.73)	1.43 (1.19-1.71)	1.23 (1.05-1.45)	1.14 (0.98-1.33)	1.29 (1.10-1.50)	1.29 (1.17-1.42)	1.27 (1.15-1.39)
Ischemic Stroke	1.17 (1.01-1.36)	1.21 (1.08-1.38)	1.14 (1.04-1.26)	1.18 (1.09-1.29)	1.26 (1.16-1.37)	1.20 (1.12-1.28)	1.20 (1.13-1.27)
VTE/PE	1.43 (1.27-1.62)	1.52 (1.37-1.69)	1.47 (1.33-1.62)	1.47 (1.33-1.62)	1.49 (1.35-1.66)	1.37 (1.30-1.43)	1.59 (1.52-1.66)

*Models were adjusted for age (in sex stratified models), sex (for age models), rural residence, and income quintile.

Table 5. Adjusted Incidence Rate Ratios for CKM Outcomes Among Young People in Ontario (2015-2019 v.s. 2006-2009/2011-2014*) by Age Group and Sex

Outcome	Age Group					Sex	
	13-18 IRR (95% CI)	19-25 IRR (95% CI)	25-30 IRR (95% CI)	31-35 IRR (95% CI)	36-40 IRR (95% CI)	Male IRR (95% CI)	Female IRR (95% CI)
Cardio-Kidney-Metabolic Risk Factors							
Hypertension	0.75 (0.70-0.79)	1.23 (1.17-1.30)	1.65 (1.55-1.75)	0.85 (0.80-0.90)	0.83 (0.78-0.87)	1.03 (0.96-1.10)	0.99 (0.92-1.06)
Diabetes	1.53 (1.36-1.72)	1.08 (0.97-1.21)	0.91 (0.82-1.01)	0.98 (0.88-1.08)	1.07 (0.97-1.18)	1.05 (0.99-1.11)	1.09 (1.03-1.16)
Hyperlipidemia	0.65 (0.57-0.75)	0.48 (0.42-0.54)	0.41 (0.36-0.46)	0.41 (0.36-0.47)	0.47 (0.41-0.53)	0.49 (0.45-0.52)	0.46 (0.43-0.49)
Smoking	1.07 (0.91-1.25)	0.89 (0.77-1.03)	0.91 (0.78-1.05)	1.13 (0.97-1.32)	1.08 (0.92-1.27)	1.14 (1.06-1.23)	0.89 (0.81-0.97)
Cardiovascular Disease Outcomes							
CAD	0.80 (0.73-0.87)	0.90 (0.83-0.98)	0.80 (0.74-0.87)	0.79 (0.73-0.85)	0.86 (0.79-0.92)	0.83 (0.79-0.88)	0.84 (0.81-0.87)
ACS	0.82 (0.75-0.89)	0.89 (0.82-0.96)	0.82 (0.76-0.89)	0.81 (0.75-0.87)	0.84 (0.78-0.91)	0.82 (0.80-0.85)	0.86 (0.83-0.89)
Arrhythmia	1.32 (1.26-1.38)	1.25 (1.19-1.31)	1.19 (1.14-1.25)	1.22 (1.17-1.28)	1.26 (1.20-1.32)	1.21 (1.18-1.25)	1.27 (1.24-1.31)
CHF	1.23 (0.98-1.53)	1.45 (1.22-1.75)	1.45 (1.24-1.70)	1.38 (1.19-1.60)	1.65 (1.42-1.92)	1.51 (1.37-1.66)	1.41 (1.28-1.54)
Ischemic Stroke	1.40 (1.21-1.61)	1.42 (1.28-1.58)	1.33 (1.21-1.45)	1.33 (1.23-1.45	1.45 (1.34-1.58)	1.44 (1.35-1.54)	1.33 (1.26-1.41)
VTE/PE	1.41 (1.25-1.60)	1.55 (1.40-1.72)	1.58 (1.44-1.74)	1.64 (1.49-1.81)	1.68 (1.52-1.86)	1.47 (1.40-1.54)	1.67 (1.60-1.75)
Chronic Kidney Disease Outcomes*							
CKD: ACR > 3	1.91 (1.72-2.13)	1.62 (1.46-1.80)	1.58 (1.43-1.76)	1.00 (0.90-1.11)	0.76 (0.68-0.85)	1.18 (1.04-1.34)	1.38 (1.22-1.56)
[a]CKD: eGFR < 60	1.96 (1.46-2.62)	1.92 (1.60-2.30)	2.00 (1.72-2.32)	1.49 (1.31-1.69)	0.93 (0.83-1.05)	1.59 (1.39-1.83)	1.40 (1.24-1.58)

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Thus, 2011-2014 is the reference period for kidney disease outcomes. Models were adjusted for age (in sex stratified models), sex (for age models), rural residence, and income quintile.

[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other

Table 6. Adjusted Incidence Rate Ratios for CKM Outcomes Among Young People in Ontario (2020-2023 v.s. 2006-2009/2011-2014*) by Age Group and Sex

Outcome	Age Group					Sex	
	13-18 IRR (95% CI)	19-25 IRR (95% CI)	25-30 IRR (95% CI)	31-35 IRR (95% CI)	36-40 IRR (95% CI)	Male IRR (95% CI)	Female IRR (95% CI)
Cardio-Kidney-Metabolic Risk Factors							
Hypertension	0.67 (0.63-0.70)	1.16 (1.09-1.23)	1.67 (1.58-1.77)	1.33 (1.26-1.40)	0.86 (0.81-0.91)	1.08 (1.01-1.15)	1.10 (1.02-1.18)
Diabetes	1.58 (1.41-1.78)	1.39 (1.24-1.56)	1.21 (1.00-1.23)	1.10 (1.00-1.22)	1.14 (1.04-1.26)	1.16 (1.09-1.23)	1.29 (1.21-1.37)
Hyperlipidemia	0.72 (0.63-0.83)	0.58 (0.51-0.66)	0.49 (0.43-0.55)	0.47 (0.41-0.53)	0.50 (0.44-0.57)	0.54 (0.51-0.58)	0.54 (0.51-0.57)
Smoking	0.56 (0.47-0.67)	0.45 (0.38-0.52)	0.47 (0.40-0.55)	0.59 (0.50-0.69)	0.62 (0.52-0.73)	0.63 (0.58-0.68)	0.45 (0.41-0.49)
Cardiovascular Disease Outcomes							
CAD	0.64 (0.58-0.70)	0.86 (0.79-0.94)	0.77 (0.71-0.84)	0.72 (0.67-0.78)	0.73 (0.68-0.79)	0.76 (0.72-0.79)	0.75 (0.72-0.78)
ACS	0.68 (0.62-0.74)	0.83 (0.77-0.90)	0.76 (0.70-0.82)	0.71 (0.66-0.76)	0.71 (0.65-0.76)	0.71 (0.68-0.74)	0.77 (0.74-0.80)
Arrhythmia	1.43 (1.36-1.50)	1.58 (1.51-1.66)	1.42 (1.35-1.49)	1.42 (1.35-1.49	1.43 (1.36-1.51)	1.37 (1.33-1.40)	1.54 (1.50-1.58)
CHF	1.40 (1.12-1.76)	1.82 (1.51-2.18)	1.85 (1.58-2.16)	1.79 (1.55-2.07)	1.92 (1.65-2.22)	1.95 (1.78-2.14)	1.66 (1.52-1.82)
Ischemic Stroke	1.45 (1.25-1.68)	1.24 (1.10-1.39)	1.27 (1.16-1.40)	1.23 (1.13-1.34)	1.22 (1.11-1.33)	1.27 (1.19-1.36)	1.25 (1.18-1.33)
VTE/PE	1.05 (0.92-1.20	1.30 (1.17-1.45)	1.39 (1.25-1.53)	1.52 (1.37-1.68)	1.50 (1.35-1.67)	1.41 (1.35-1.48)	1.34 (1.27-1.40)
Chronic Kidney Disease Outcomes*							
CKD: ACR > 3	4.34 (3.90-4.83)	2.86 (2.57-3.19)	2.62 (2.36-2.91)	1.28 (1.15-1.42)	0.66 (0.59-0.73)	1.78 (1.56-2.02)	2.20 (1.95-2.49)
[a]CKD: eGFR < 60	4.09 (3.04-5.49)	2.13 (1.76-2.58)	2.65 (2.29-3.08)	1.82 (1.60-2.06)	0.83 (0.74-0.94)	1.83 (1.59-2.11)	1.66 (1.47-1.87)

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Thus, 2011-2014 is the reference period for kidney disease outcomes. Models were adjusted for age (in sex stratified models), sex (for age models), rural residence, and income quintile.

[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Table 7. Age Group x Era Interaction *p*-values

Outcome	Interaction *p*-value
Cardio-Kidney-Metabolic Risk Factors	
Hypertension	< .0001
Diabetes	< .0001
Hyperlipidemia	< .0001
Smoking	0.13
Cardiovascular Disease Outcomes	
CAD	0.0003
ACS	0.004
Arrhythmia	< .0001
CHF	0.03
Ischemic Stroke	0.16
VTE/PE	0.002
Chronic Kidney Disease Outcomes*	
CKD: ACR > 3	< .0001
[a]CKD: eGFR > 60	< .0001

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Thus, 2011-2014 is the reference period for kidney disease outcomes. Models were adjusted for sex, rural residence, and income quintile.
[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

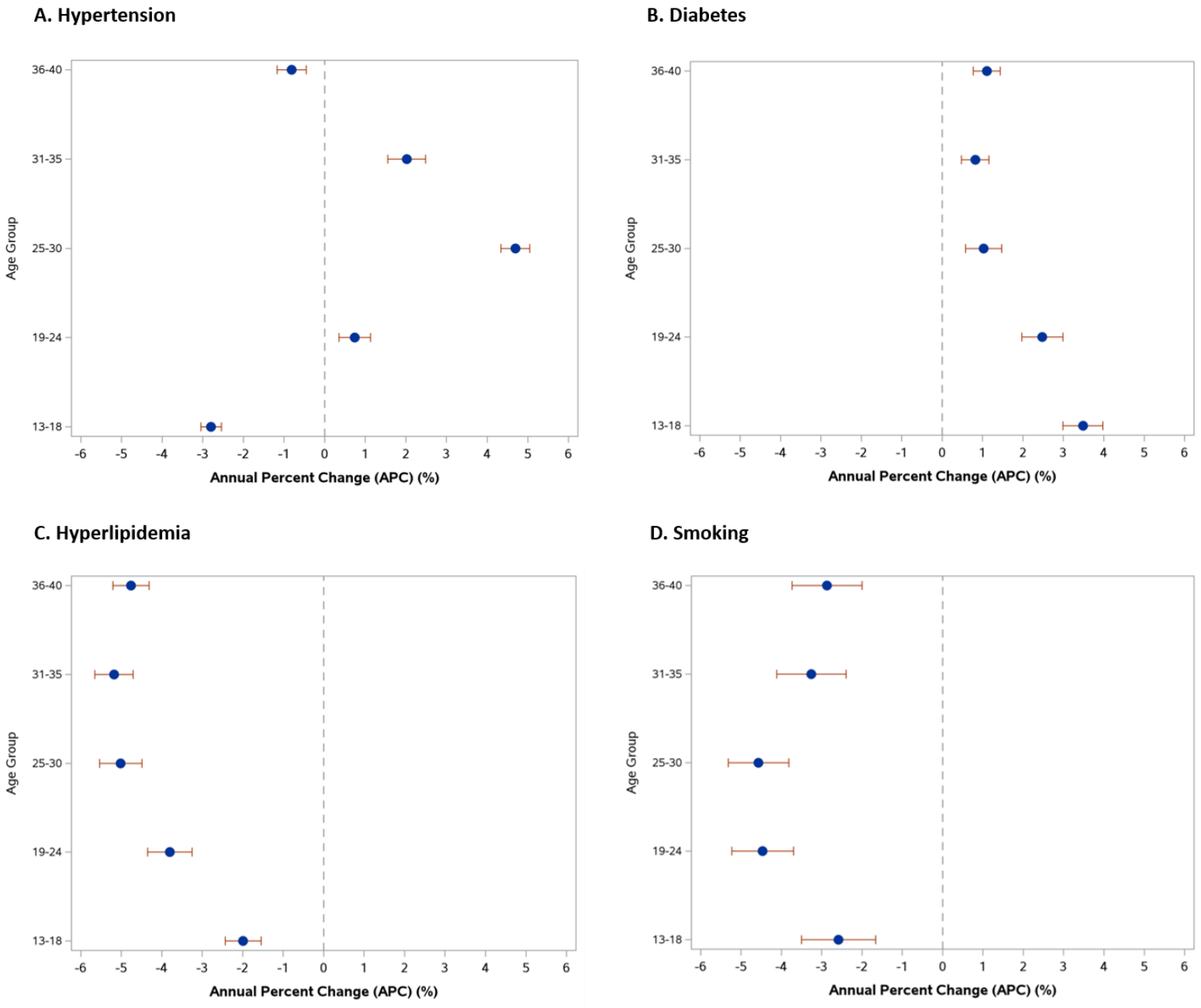
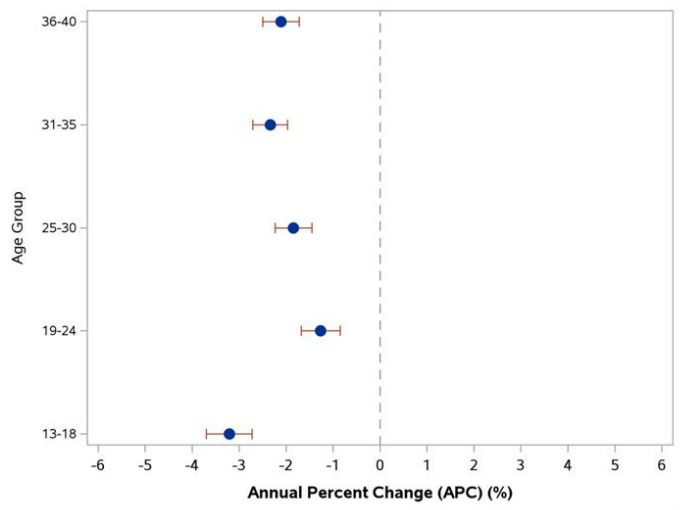
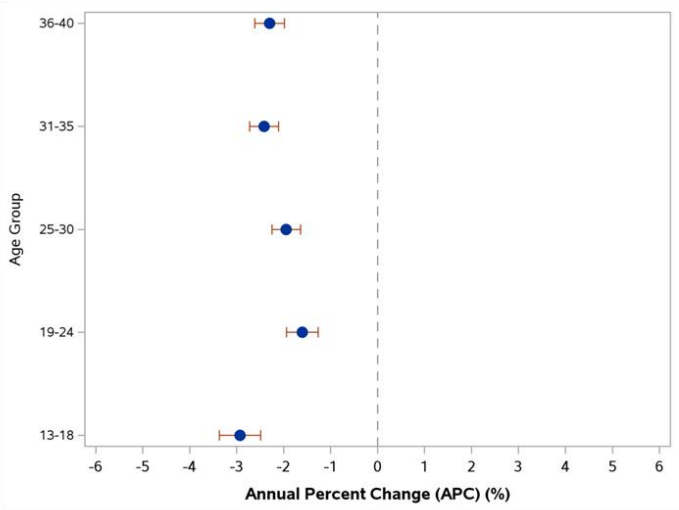


Figure 14. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKM Risk Factors

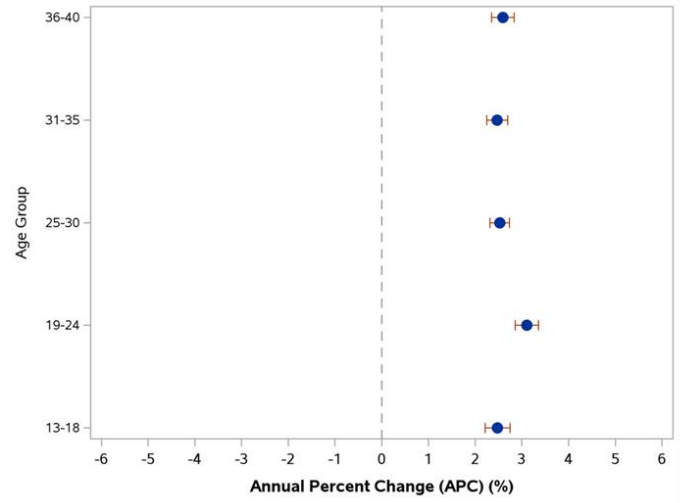
A. Coronary Artery Disease (CAD)



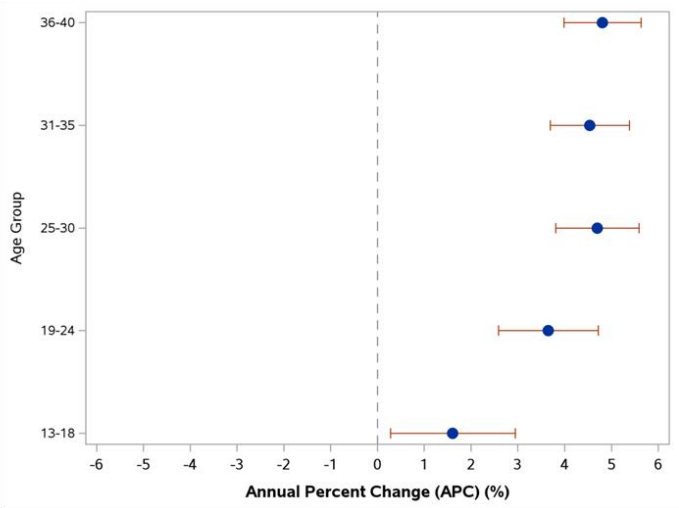
B. Acute Coronary Syndrome (ACS)



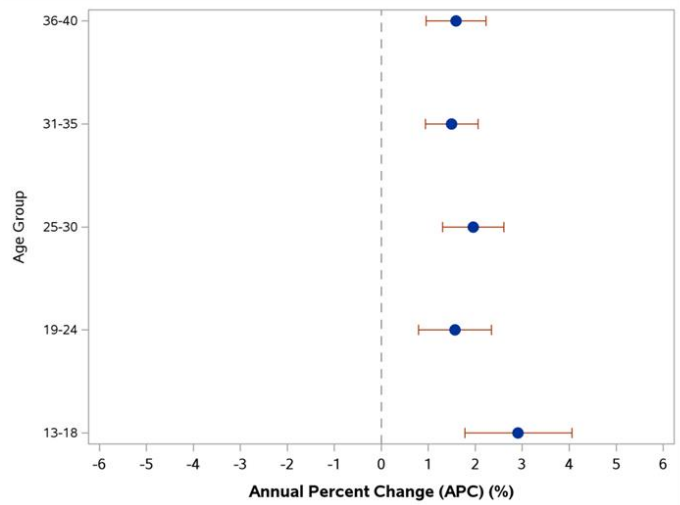
C. Arrhythmia



D. Congestive Heart Failure (CHF)



E. Ischemic Stroke



F. Venous Thromboembolism/Pulmonary Embolism (VTE/PE)

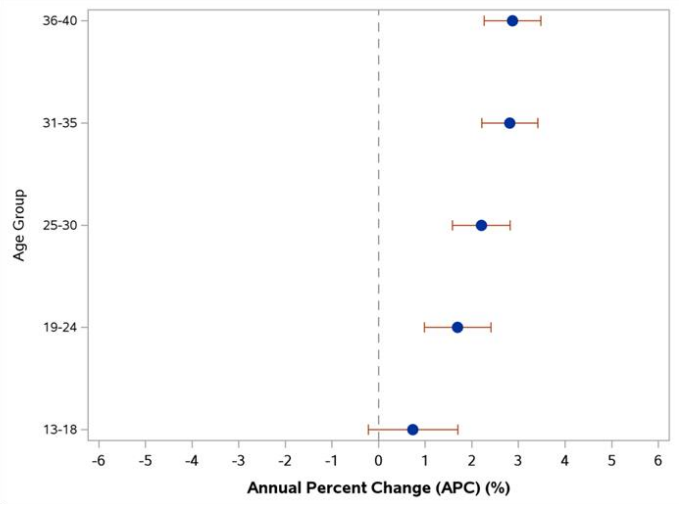
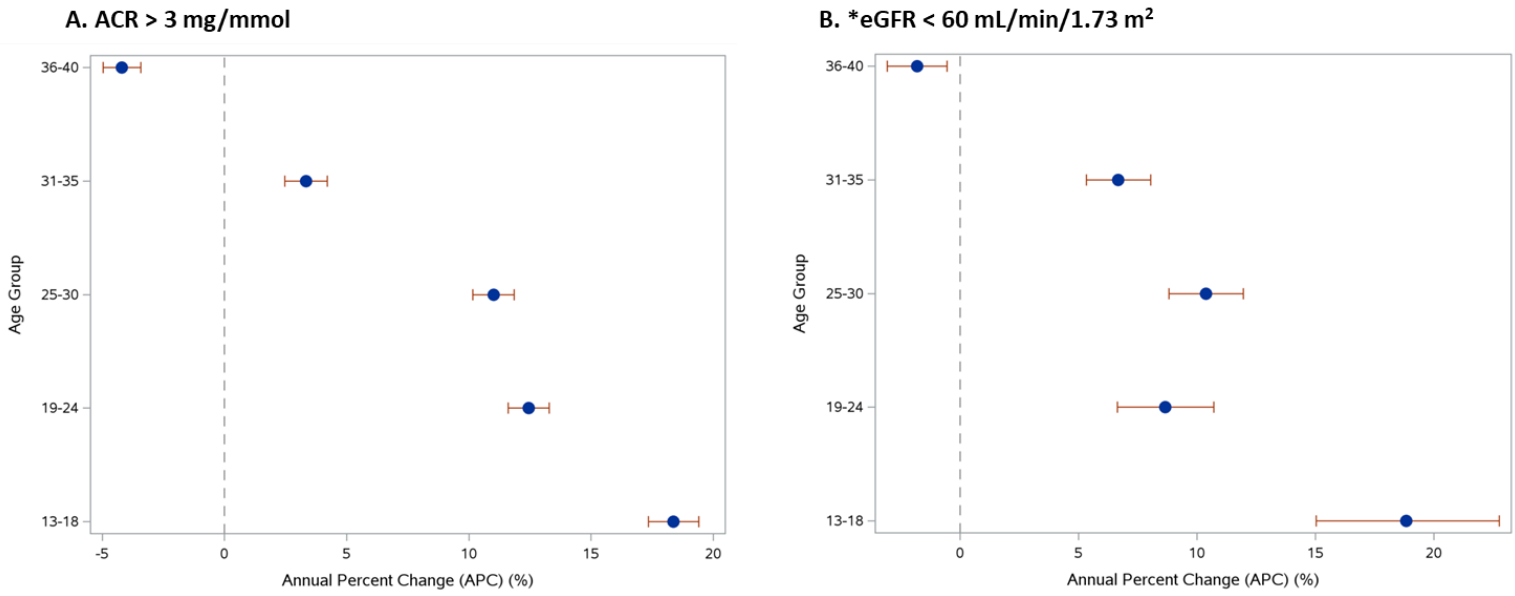


Figure 15. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CV Diseases



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

Figure 16. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKD Indicators

Table 8. Average Annual Percent Change in Incidence by Age Group, 2006–2023

Outcome	Average Annual Percent Change, % (95% CI)				
	13-18	**19-24**	**25-30**	**31-35**	**36-40**
Cardio-Kidney-Metabolic Risk Factors					
Hypertension	-2.8 (-3.1, -2.5)	0.7 (0.4, 1.1)	4.7 (4.3, 5.1)	2.0 (1.6, 2.5)	-0.8 (-1.2, -0.5)
Diabetes	3.5 (3.0, 4.0)	2.5 (2.0, 3.0)	1.0 (0.6, 1.5)	0.8 (0.5, 1.2)	1.1 (0.8, 1.4)
Hyperlipidemia	-2.0 (-2.4, -1.6)	-3.8 (-4.4, -3.3)	-5.0 (-5.5, -4.5)	-5.2 (-5.7, -4.7)	-4.8 (-5.2, -4.3)
Smoking	-2.6 (-3.5, -1.7)	-4.5 (-5.2, -3.7)	-4.6 (-5.3, -3.8)	-3.3 (-4.1, -2.4)	-2.9 (-3.7, -2.0)
Cardiovascular Disease Outcomes					
CAD	-3.2 (-3.7, -2.7)	-1.3 (-1.7, -0.9)	-1.8 (-2.2, -1.5)	-2.3 (-2.7, -2.0)	-2.1 (-2.5, -1.7)
ACS	-2.9 (-3.4, -2.5)	-1.6 (-1.9, -1.3)	-2.0 (-2.3, -1.6)	-2.4 (-2.7, -2.1)	-2.3 (-2.6, -2.0)
Arrhythmia	2.5 (2.2, 2.8)	3.1 (2.9, 3.4)	2.5 (2.3, 2.7)	2.5 (2.3, 2.7)	2.6 (2.4, 2.8)
CHF	1.6 (0.3, 3.0)	3.7 (2.6, 4.7)	4.7 (3.8, 5.6)	4.5 (3.7, 5.4)	4.8 (4.0, 5.6)
Ischemic Stroke	2.9 (1.8, 4.1)	1.6 (0.8, 2.3)	2.0 (1.3, 2.6)	1.5 (0.9, 2.1)	1.6 (1.0, 2.2)
VTE/PE	0.7 (-0.2, 1.7)	1.7 (1.0, 2.4)	2.2 (1.6, 2.8)	2.8 (2.2, 3.4)	2.9 (2.3, 3.5)
Chronic Kidney Disease Outcomes*					
CKD: ACR > 3	18.4 (17.4, 19.4)	12.5 (11.6, 13.3)	11.0 (10.2, 11.9)	3.3 (2.5, 4.2)	-4.2 (-5.0, -3.4)
[a]CKD: eGFR < 60	18.8 (15.0, 22.8)	8.7 (6.6, 10.7)	10.4 (8.8, 12.0)	6.7 (5.3, 8.1)	-1.8 (-3.1, -0.5)

*Analysis of ACR and eGFR measures starts in 2011 to allow for OLIS catch-up. Thus average annual percent change for these indicators is from 2011-2023. Models were adjusted for sex, rural residence, and income quintile.

[a]CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.

CHAPTER 4: Discussion

This retrospective population-based cohort study included over 5.6 million adolescents and young adults living in Ontario, aged 13-40 years old. Results revealed that while incidence rates of traditional cardio-kidney-metabolic risk factors and outcomes (hyperlipidemia, smoking, CAD, ACS) have generally declined over time, there has been significant increases in the incidence of conditions such as diabetes, arrhythmia, CHF, VTE/PE, and both CKD indicators that have occurred in this population. Furthermore, age stratified analysis demonstrate that for several CKM outcomes, such as diabetes, arrhythmia, elevated ACR, and reduced eGFR, the largest increases are occurring amongst the youngest age groups (13-24 year olds). These findings suggest that there may be a shifting burden of CKM disease in younger populations compared to the profile of CKM disease observed in previous generations.

Previous research highlight trends that are fairly consistent with the findings of our study. With respect to CKM risk factors, an increase in the incidence of diabetes amongst children and adolescents over the years has been observed in both Canada and the United States (41,42). Similar to the results of our study, a prospective cohort study analyzing diabetes in Canadian children under 18 found that the incidence was 60% higher in 2017-2019 than it was in 2006-2008 (41). Moreover, a study using data from the Canadian Health Measures Survey (CHMS) found large increases in hypertension amongst 20 to 39 year olds following the COVID-19 pandemic (43), whereas this study found significant increases in the post-pandemic era (2020-2023) for those aged 19 to 35 years old—both underscoring a concerning trend for young adults. Hyperlipidemia was the most prevalent risk factor throughout the entire period, although incidence rates were observed to have steadily declined over time. A study out of the U.S. highlighted that while self-reported hyperlipidemia increased over time amongst young adults,

the number of individuals diagnosed using clinical criteria has declined (44). Given that our study cohort is comprised of adolescents and young adults, a demographic which is not routinely assessed for hyperlipidemia, it may be that a lower number of incident cases are being flagged due to overall less screening of these individuals.

Interestingly in regard to CV conditions, our study found significant increases in the incidence of non-atherosclerotic conditions such as arrhythmia, CHF, and VTE/PE compared to atherosclerotic diseases like CAD and ACS. Similarly, other studies have found there to be a steady rise in arrhythmia and heart failure in younger populations (45–47). A recent Canadian study found that hospitalizations for heart failure significantly increased amongst those aged 20-39 years old between 2007 to 2016 (47), with our study demonstrating that incident cases continued to climb after 2020 in this group. The burden of common arrhythmias such as atrial fibrillation and flutter also increased around the world amongst adolescents and young adults, with incidence and related mortality increasing by approximately 57% and 71% respectively from 1990 to 2021 (45). Even while overall incidence may be low, significant increases over time poses a concerning trajectory for these diseases and also suggests that the makeup of CVD burden in young people may be shifting—a trend that was also observed in adults from the United Kingdom (48). Furthermore, research suggests that increases in these conditions amongst adolescent and young adults are attributable to a rise in risk factors. A significant number of younger adults with atrial fibrillation also were comorbid for obesity, smoking, diabetes, and hypertension (49). The risk of developing conditions such as VTE and ischemic stroke (both of which saw increases in incidence across eras in our study) are also associated with common CKM risk factors (50,51). Although our study did not assess causal relationships or associations

between disease outcomes, it is notable to report that increases in CKM risk factors such as diabetes and hypertension were observed in tandem with the rise in these CV conditions.

Among those that were tested, the dramatic rise in CKD indicators (having an elevated ACR (> 3 mg/mmol) and/or reduced eGFR (< 60 mL/min/1.73 m^2) levels), particularly amongst youth aged 13-18 years old was a striking finding in this study. The literature does suggest that there has been a significant increase in CKD burden in youth over the years (52,53), and that having risk factors such as hypertension and diabetes contribute to the development of CKD in children and adolescents (54,55). Again, our study did not analyze associations but found a significant rise in diabetes within 13-18 year olds as well (although hypertension incidence was found to have decreased across eras). It is important to note that analysis of trends in CKD was done using data from individuals who had ACR and or eGFR measured. These laboratory tests are not universally conducted in youth and are usually targeted for those deemed at risk. More research is needed to fully understand the health profile of those presenting with CKD indicators and whether these trends exist more broadly in the general population.

In all, the findings from this study underscore the need to prioritize younger populations, particularly adolescents, when it comes to prevention and disease mitigation. It is known that having suboptimal health and health behaviours in adolescence can contribute to adverse health outcomes later in adulthood (56,57), particularly concerning the development of heart and kidney disease (58–60). While existing therapies can treat progressing CKM disease in its various stages, earlier recognition and management of critical risk factors is essential for overall disease prevention and burden reduction. Furthermore, attention should be paid to the specific types of CKM diseases manifesting in this population, as there appears to be a shift from traditional atherosclerotic diseases. Future health policies should focus on addressing potential gaps and

barriers to early screening, which may prove to be beneficial in better determining who is at risk and how their risk can be mitigated (61,62). Raising awareness of CKM risk factors and disease in younger populations should also be prioritized, as this can potentially increase engagement with healthcare providers and services and improve early detection (63).

Strengths and Limitations

To our knowledge, this is the first study to conduct a comprehensive analysis on trends in CKM risk factors and disease outcomes using population-level data in young Ontarians. By studying how trends in risk factors, CV disease, and kidney disease outcomes have changed all together, it allows for a better understanding of how CKM disease burden has changed over time in this key sub population—especially given that these three facets of health are strongly connected with one another. The large and representative cohort size as well as the long follow-up period in this study also provides a fuller picture of the current status in CKM health in young people living in Ontario. However, there are several limitations in this study to address. Firstly, the occurrence of outcomes of interest were based on healthcare utilization of the cohort. Although validated ICD codes and a comprehensive set of databases (such as NACRS, SDS, and OHIP) were used to capture these encounters, it is worth noting that a younger population has less healthcare encounters compared to their older counterparts and are not routinely screened for many diseases. This may result in missed cases and an underestimation of true disease prevalence/incidence. However, given that many of our findings are consistent with what has been reported in the literature, the risk of under capturing appears to be mitigated. Secondly, ICD codes to determine trends in smoking lack sensitivity and may not fully capture true cases compared to the codes for other outcomes and thus should be interpreted with some caution. However, the decline in smoking incidence observed in our study is consistent with results from

multiple studies that have demonstrated the significant and substantial decrease in smoking amongst Canadians over the years (64,65). Additionally, OLIS implementation and capture increased throughout the study period and should be acknowledged in the interpretation of CKD results (66). Although our findings are consistent with research indicating an increase in different CKM outcomes over the years, the effects of increased and improved testing should not be ignored. Additionally, it is important to note that medication use amongst individuals was not accounted for in this study as data on medication use for Ontarians through ICES is not widely available for those under 65 years of age. This should be kept in mind when interpreting the results of CKD related outcomes (which were based on laboratory tests), as medication use can influence testing frequency. Finally, as alluded to before, this study is an observational study and therefore conclusions about the underlying mechanisms behind emerging disease patterns cannot be made.

Conclusion

In this population-based cohort study of Ontarian adolescents and young adults, we found an increased incidence of numerous critical CKM risk factors, CV conditions, and CKD indicators over approximately the past two decades. Despite some modest declines in other outcomes, our findings suggest that there is an evolving and growing burden of CKM disease in younger individuals and highlights the need for earlier identification and prevention, in order to reduce the future burden of illness as this population continues to age. If individuals are experiencing CKM risk factors and subsequent cardiac and kidney disease at an earlier age, the consequences of this could include the need for severe treatments, experience of comorbid conditions and/or death earlier in life. Thus, there should be emphasis on prevention and potential early screening for this population. Finally, as this study centers solely on observed trends, future research

should focus on the factors that are driving this observed increase in CKM disease and the mechanistic patterns behind disease development in order to broaden our understanding of this phenomenon.

References

1. Canada PHA of. Surveillance of heart diseases and conditions [education and awareness] [Internet]. 2017 [cited 2025 May 31]. Available from: https://www.canada.ca/en/public-health/services/diseases/heart-health/heart-diseases-conditions/surveillance-heart-diseases-conditions.html

2. Bello AK, Ronksley PE, Tangri N, Kurzawa J, Osman MA, Singer A, et al. Prevalence and Demographics of CKD in Canadian Primary Care Practices: A Cross-sectional Study. Kidney Int Rep. 2019 Jan 21;4(4):561–70. doi:10.1016/j.ekir.2019.01.005 PubMed PMID: 30993231; PubMed Central PMCID: PMC6451150.

3. Government of Canada SC. Diabetes prevalence, awareness, treatment and control, combined cycles, by age group and sex, Canada (excluding territories) [Internet]. 2023 [cited 2025 May 31]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310087301

4. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardio-metabolic risk factors between 1980 and 2010: comparative risk assessment. Lancet Diabetes Endocrinol. 2014 Aug;2(8):634–47. doi:10.1016/S2213-8587(14)70102-0 PubMed PMID: 24842598; PubMed Central PMCID: PMC4572741.

5. Sarafidis P, Ferro CJ, Morales E, Ortiz A, Malyszko J, Hojs R, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2019 Feb 1;34(2):208–30. doi:10.1093/ndt/gfy407 PubMed PMID: 30753708.

6. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int J Mol Sci. 2019 May 13;20(9):2358. doi:10.3390/ijms20092358 PubMed PMID: 31085992; PubMed Central PMCID: PMC6539070.

7. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, Adipose Tissue and Vascular Dysfunction. Circ Res. 2021 Apr 2;128(7):951–68. doi:10.1161/CIRCRESAHA.121.318093 PubMed PMID: 33793327; PubMed Central PMCID: PMC8026272.

8. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: The Framingham Heart Study. Circulation. 2010 Feb 2;121(4):505–11. doi:10.1161/CIRCULATIONAHA.109.886655 PubMed PMID: 20083680; PubMed Central PMCID: PMC2836717.

9. Khayyat-Kholghi M, Oparil S, Davis BR, Tereshchenko LG. Worsening kidney function is the major mechanism of heart failure in hypertension: the ALLHAT study. JACC Heart Fail. 2021 Feb;9(2):100–11. doi:10.1016/j.jchf.2020.09.006 PubMed PMID: 33189627; PubMed Central PMCID: PMC7855256.

10. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023 Nov 14;148(20):1606–35. doi:10.1161/CIR.0000000000001184

11. Brown CL, Halvorson EE, Cohen GM, Lazorick S, Skelton JA. Addressing Childhood Obesity: Opportunities for Prevention. Pediatr Clin North Am. 2015 Oct;62(5):1241–61. doi:10.1016/j.pcl.2015.05.013 PubMed PMID: 26318950; PubMed Central PMCID: PMC4555982.

12. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney Disease and Increased Mortality Risk in Type 2 Diabetes. J Am Soc Nephrol JASN. 2013 Jan 31;24(2):302–8. doi:10.1681/ASN.2012070718 PubMed PMID: 23362314; PubMed Central PMCID: PMC3559486.

13. Ostrominski JW, Arnold SV, Butler J, Fonarow GC, Hirsch JS, Palli SR, et al. Prevalence and Overlap of Cardiac, Renal, and Metabolic Conditions in US Adults, 1999-2020. JAMA Cardiol. 2023 Nov;8(11):1050–60. doi:10.1001/jamacardio.2023.3241 PubMed PMID: 37755728; PubMed Central PMCID: PMC10535010.

14. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001 Sep 20;345(12):851–60. doi:10.1056/NEJMoa011303 PubMed PMID: 11565517.

15. McCoy RG, Herrin J, Swarna KS, Deng Y, Kent DM, Ross JS, et al. Effectiveness of glucose-lowering medications on cardiovascular outcomes in patients with type 2 diabetes at moderate cardiovascular risk. Nat Cardiovasc Res. 2024 Apr;3(4):431–40. doi:10.1038/s44161-024-00453-9 PubMed PMID: 38846711; PubMed Central PMCID: PMC11156225.

16. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet Lond Engl. 2016 Mar 5;387(10022):957–67. doi:10.1016/S0140-6736(15)01225-8 PubMed PMID: 26724178.

17. Liu JJ, Liu S, Gurung RL, Ang K, Tang WE, Sum CF, et al. Risk of progressive chronic kidney disease in individuals with early-onset type 2 diabetes: a prospective cohort study. Nephrol Dial Transplant. 2020 Jan 1;35(1):115–21. doi:10.1093/ndt/gfy211

18. Jacobs DR, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, et al. Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events. N Engl J Med. 2022 May 19;386(20):1877–88. doi:10.1056/NEJMoa2109191 PubMed PMID: 35373933; PubMed Central PMCID: PMC9563825.

19. Anderson LN, Islam R, Sweetman A. Trends in obesity defined by body mass index among adults before and during the COVID-19 pandemic: a repeated cross-sectional study of the

2009–2023 Canadian Community Heath Surveys. CMAJ. 2025 Jul 14;197(25):E708–18. doi:10.1503/cmaj.241421 PubMed PMID: 40659454.

20. Government of Canada SC. The Daily — The prevalence of overweight and obesity is on the rise in Canada: New results from the Canadian Health Measures Survey, 2022 to 2024 [Internet]. 2025 [cited 2025 Oct 23]. Available from: https://www150.statcan.gc.ca/n1/daily-quotidien/251002/dq251002b-eng.htm

21. Alshammri F, Geddie H, Sawalha N, Kim G, McAssey K, Morrison KM. Factors Associated With the Development of Dyslipidemia Among Pediatric Patients With Diabetes: A Single-centre–based Study. Can J Diabetes. 2023 Oct 1;47(7):611–7. doi:10.1016/j.jcjd.2023.06.003

22. Robinson CH, Hussain J, Jeyakumar N, Smith G, Birken CS, Dart A, et al. Long-Term Cardiovascular Outcomes in Children and Adolescents With Hypertension. JAMA Pediatr. 2024 Jul;178(7):688–98. doi:10.1001/jamapediatrics.2024.1543 PubMed PMID: 38709137; PubMed Central PMCID: PMC11217870.

23. McCrindle BW, Manlhiot C, Millar K, Gibson D, Stearne K, Kilty H, et al. Population Trends Toward Increasing Cardiovascular Risk Factors in Canadian Adolescents. J Pediatr. 2010 Nov 1;157(5):837–43. doi:10.1016/j.jpeds.2010.05.014 PubMed PMID: 20955854.

24. Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascular Risk Factor Prevalence, Treatment, and Control in US Adults Aged 20 to 44 Years, 2009 to March 2020. JAMA. 2023 Mar 21;329(11):899–909. doi:10.1001/jama.2023.2307 PubMed PMID: 36871237; PubMed Central PMCID: PMC9986841.

25. Tarride JE, Lim M, DesMeules M, Luo W, Burke N, O'Reilly D, et al. A review of the cost of cardiovascular disease. Can J Cardiol. 2009 Jun;25(6):e195–202. doi:10.1016/S0828-282X(09)70098-4

26. Government of Canada SC. Leading causes of death, total population, by age group [Internet]. 2021 [cited 2025 Oct 24]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401

27. Brunham LR, Lonn E, Mehta SR. Dyslipidemia and the Current State of Cardiovascular Disease: Epidemiology, Risk Factors, and Effect of Lipid Lowering. Can J Cardiol. 2024 Aug 1;40(8):S4–12. doi:10.1016/j.cjca.2024.04.017 PubMed PMID: 39111899.

28. Vikulova DN, Grubisic M, Zhao Y, Lynch K, Humphries KH, Pimstone SN, et al. Premature Atherosclerotic Cardiovascular Disease: Trends in Incidence, Risk Factors, and Sex-Related Differences, 2000 to 2016. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2019 Jul 8;8(14):e012178. doi:10.1161/JAHA.119.012178 PubMed PMID: 31280642; PubMed Central PMCID: PMC6662126.

29. Sun J, Qiao Y, Zhao M, Magnussen CG, Xi B. Global, regional, and national burden of cardiovascular diseases in youths and young adults aged 15–39 years in 204 countries/territories, 1990–2019: a systematic analysis of Global Burden of Disease Study

2019. BMC Med. 2023 Jun 26;21:222. doi:10.1186/s12916-023-02925-4 PubMed PMID: 37365627; PubMed Central PMCID: PMC10294522.

30. 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 Feb 13;10:20543581231154185. doi:10.1177/20543581231154185 PubMed PMID: 36798634; PubMed Central PMCID: PMC9926383.

31. Manns B, McKenzie SQ, Au F, Gignac PM, Geller LI. The Financial Impact of Advanced Kidney Disease on Canada Pension Plan and Private Disability Insurance Costs. Can J Kidney Health Dis. 2017 Apr 17;4:2054358117703986. doi:10.1177/2054358117703986 PubMed PMID: 28491340; PubMed Central PMCID: PMC5406196.

32. Organ replacement in Canada: CORR annual statistics | CIHI [Internet]. [cited 2025 Oct 24]. Available from: https://www.cihi.ca/en/organ-replacement-in-canada-corr-annual-statistics

33. Bowe B, Xie Y, Li T, Mokdad AH, Xian H, Yan Y, et al. Changes in the US Burden of Chronic Kidney Disease From 2002 to 2016. JAMA Netw Open. 2018 Nov 30;1(7):e184412. doi:10.1001/jamanetworkopen.2018.4412 PubMed PMID: 30646390; PubMed Central PMCID: PMC6324659.

34. Sun P, Ming X, Song T, Chen Y, Yang X, Sun Z, et al. Global burden of chronic kidney disease in adolescents and young adults, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Front Endocrinol. 2024 Sep 18;15:1389342. doi:10.3389/fendo.2024.1389342 PubMed PMID: 39359410; PubMed Central PMCID: PMC11445070.

35. Kazi DS, Elkind MSV, Deutsch A, Dowd WN, Heidenreich P, Khavjou O, et al. Forecasting the Economic Burden of Cardiovascular Disease and Stroke in the United States Through 2050: A Presidential Advisory From the American Heart Association. Circulation. 2024 Jul 23;150(4):e89–101. doi:10.1161/CIR.0000000000001258

36. Shahid I, Philip J, Avenatti E, Laddu D, Shapiro MD, Khera A, et al. Lifestyle Interventions in Cardiovascular-Kidney-Metabolic Syndrome JACC: Advances Expert Panel. JACC Adv. 2025 Jun 25;4(6):101788. doi:10.1016/j.jacadv.2025.101788 PubMed PMID: 40579052; PubMed Central PMCID: PMC12277609.

37. Noubiap JJ, Nyaga UF. Cardiovascular disease prevention should start in early life. BMC Glob Public Health. 2023 Sep 7;1(1):14. doi:10.1186/s44263-023-00015-4

38. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction. Circulation. 2010 Feb 2;121(4):586–613. doi:10.1161/CIRCULATIONAHA.109.192703

39. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344–9. doi:10.1016/j.jclinepi.2007.11.008 PubMed PMID: 18313558.

40. ICES | About ICES Data. ICES [Internet]. [cited 2025 May 31]. Available from: https://www.ices.on.ca/about-ices-data/

41. Patel TJ, Ayub A, Bone JN, Hadjiyannakis S, Henderson M, Nour MA, et al. Incidence Trends of Type 2 Diabetes Mellitus, Medication-Induced Diabetes, and Monogenic Diabetes in Canadian Children, Then (2006–2008) and Now (2017–2019). Pediatr Diabetes. 2023;2023(1):5511049. doi:10.1155/2023/5511049

42. Mefford MT, Wei R, Lustigova E, Martin JP, Reynolds K. Incidence of Diabetes Among Youth Before and During the COVID-19 Pandemic. JAMA Netw Open. 2023 Sep 21;6(9):e2334953. doi:10.1001/jamanetworkopen.2023.34953

43. McAlister FA, Bushnik T, Leung AA. Changes in Hypertension Prevalence and Control in Canada After the COVID-19 Pandemic: Insights From the Canadian Health Measures Survey Cycle 7. Can J Cardiol. 2026 Apr 22;S0828-282X(26)00370-3. doi:10.1016/j.cjca.2026.04.013 PubMed PMID: 42031107.

44. Leppert MH, Poisson SN, Sillau SH, Campbell JD, Ho PM, Burke JF. Is Prevalence of Atherosclerotic Risk Factors Increasing Among Young Adults? It Depends on How You Ask. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2019 Mar 12;8(6):e010883. doi:10.1161/JAHA.118.010883 PubMed PMID: 30857455; PubMed Central PMCID: PMC6475043.

45. Zhang X, Chen Y, Hu W, Lu S, Yu H, Sun Y. Global burden of atrial fibrillation/atrial flutter and its attributable risk factors in adolescents and young adults, 1990–2021: insights from the global burden of disease study. Ann Med. 57(1):2543524. doi:10.1080/07853890.2025.2543524 PubMed PMID: 40761146; PubMed Central PMCID: PMC12326374.

46. Yang C, Jia Y, Zhang C, Jin Z, Ma Y, Bi X, et al. Global, regional, and national burdens of heart failure in adolescents and young adults aged 10–24 years from 1990 to 2021: an analysis of data from the Global Burden of Disease Study 2021. eClinicalMedicine. 2024 Dec 9;79:102998. doi:10.1016/j.eclinm.2024.102998 PubMed PMID: 39737218; PubMed Central PMCID: PMC11683260.

47. Botly LCP, Lindsay MP, Mulvagh SL, Hill MD, Goia C, Martin-Rhee M, et al. Recent Trends in Hospitalizations for Cardiovascular Disease, Stroke, and Vascular Cognitive Impairment in Canada. Can J Cardiol. 2020 Jul 1;36(7):1081–90. doi:10.1016/j.cjca.2020.03.007 PubMed PMID: 32622652.

48. Conrad N, Molenberghs G, Verbeke G, Zaccardi F, Lawson C, Friday JM, et al. Trends in cardiovascular disease incidence among 22 million people in the UK over 20 years: population based study. The BMJ. 2024 Jun 26;385:e078523. doi:10.1136/bmj-2023-078523 PubMed PMID: 38925788; PubMed Central PMCID: PMC11203392.

49. Bhonsale A, Zhu J, Thoma F, Koscumb S, Kancharla K, Voigt A, et al. Mortality, Hospitalization, and Cardiac Interventions in Patients With Atrial Fibrillation Aged <65 Years. Circ Arrhythm Electrophysiol. 2024 May;17(5):e012143. doi:10.1161/CIRCEP.123.012143

50. Aigner A, Grittner U, Rolfs A, Norrving B, Siegerink B, Busch MA. Contribution of Established Stroke Risk Factors to the Burden of Stroke in Young Adults. Stroke. 2017 Jul;48(7):1744–51. doi:10.1161/STROKEAHA.117.016599 PubMed PMID: 28619986.

51. Stein PD, Goldman J, Matta F, Yaekoub AY. Diabetes mellitus and risk of venous thromboembolism. Am J Med Sci. 2009 Apr;337(4):259–64. doi:10.1097/MAJ.0b013e31818bbb8b PubMed PMID: 19365171.

52. Majoni M, Gardiner H, Robitaille C. PREVALENCE ESTIMATES OF CHRONIC KIDNEY DISEASE AND ASSOCIATED COMORBIDITIES: RESULTS FROM THE CANADIAN HEALTH MEASURES SURVEY. Can J Cardiol. 2023 Oct 1;39(10):S92–3. doi:10.1016/j.cjca.2023.06.138

53. Zhao WM, Li XL, Shi R, Zhu Y, Wang ZJ, Wang XR, et al. Global, regional and national burden of CKD in children and adolescents from 1990 to 2019. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2024 Jul 31;39(8):1268–78. doi:10.1093/ndt/gfad269 PubMed PMID: 38130213.

54. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, et al. Blood Pressure in Children with Chronic Kidney Disease: A Report from the Chronic Kidney Disease in Children Study. Hypertension. 2008 Oct;52(4):631–7. doi:10.1161/HYPERTENSIONAHA.108.110635 PubMed PMID: 18725579; PubMed Central PMCID: PMC3136362.

55. Dart AB, Sellers EA, Martens PJ, Rigatto C, Brownell MD, Dean HJ. High Burden of Kidney Disease in Youth-Onset Type 2 Diabetes. Diabetes Care. 2012 Jun;35(6):1265–71. doi:10.2337/dc11-2312 PubMed PMID: 22432116; PubMed Central PMCID: PMC3357249.

56. TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021 Jul 29;385(5):416–26. doi:10.1056/NEJMoa2100165 PubMed PMID: 34320286; PubMed Central PMCID: PMC8697255.

57. Amialchuk A, Sapci O. The long-term health effects of initiating smoking in adolescence: Evidence from a national longitudinal survey. Health Econ. 2022;31(4):597–613. doi:10.1002/hec.4469

58. Guo JW, Ning H, Allen NB, Perak AM, Walker JM, Pettee Gabriel K, et al. Cardiovascular Health Changes in Young Adults and Risk of Later-Life Cardiovascular Disease. JAMA Netw Open. 2025 Oct 6;8(10):e2535573. doi:10.1001/jamanetworkopen.2025.35573 PubMed PMID: 41051778; PubMed Central PMCID: PMC12501802.

59. Robinson CH, Hussain J, Jeyakumar N, Smith G, Birken CS, Dart A, et al. Long-Term Cardiovascular Outcomes in Children and Adolescents With Hypertension. JAMA Pediatr. 2024 Jul;178(7):688–98. doi:10.1001/jamapediatrics.2024.1543 PubMed PMID: 38709137; PubMed Central PMCID: PMC11217870.

60. Hussain J, Georgieva K, Robinson CH, Jeyakumar N, Smith G, Brady T, et al. Long-term kidney outcomes in children and adolescents with hypertension: a propensity-matched cohort study. Lancet Child Adolesc Health. 2025 Aug 1;9(8):553–64. doi:10.1016/S2352-4642(25)00127-0

61. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023 Nov 14;148(20):1636–64. doi:10.1161/CIR.0000000000001186

62. Khoury M, Ware AL, McCrindle BW. The prevention of adult cardiovascular disease must begin in childhood: evidence and imperative. Nat Rev Cardiol. 2026 Apr;23(4):279–92. doi:10.1038/s41569-025-01209-z PubMed PMID: 40940549.

63. Hemmelgarn BR, Pannu N, Ahmed SB, Elliott MJ, Tam-Tham H, Lillie E, et al. Determining the research priorities for patients with chronic kidney disease not on dialysis. Nephrol Dial Transplant. 2017 May;32(5):847–54. doi:10.1093/ndt/gfw065 PubMed PMID: 27190349; PubMed Central PMCID: PMC5837625.

64. Canada H. Canadian Tobacco and Nicotine Survey (CTNS): summary of results for 2020 [surveys] [Internet]. 2022 [cited 2026 Jul 31]. Available from: https://www.canada.ca/en/health-canada/services/canadian-tobacco-nicotine-survey/2020-summary.html

65. Historical trends in smoking prevalence | Tobacco Use in Canada | University of Waterloo [Internet]. [cited 2026 Jul 31]. Available from: https://uwaterloo.ca/tobacco-use-canada/adult-tobacco-use/smoking-canada/historical-trends-smoking-prevalence

66. Iskander C, McArthur E, Nash DM, Gandhi-Banga S, Weir MA, Muanda FT, et al. Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a descriptive study. CMAJ Open. 2019;7(4):E624–9. doi:10.9778/cmajo.20190065 PubMed PMID: 31641060; PubMed Central PMCID: PMC6944071.

Supplementary Materials

Table S1. ICES Databases Used and Accessed in this Study

Canadian Institute of Health Information – Discharge Abstract Database (CIHI-DAD)	Contains administrative and clinical data for all acute hospital admissions and discharges including demographic, diagnostic, and procedural variables.
Ontario Health Insurance Plan (OHIP)	Records of claims for physician services covered by the Ontario government. OHIP fee and diagnostic codes cover the specific services (inpatient, outpatient. etc.) provided to the patient.
Registered Persons Database (RPDB)	Information on demographic characteristics (age, sex, residence (using postal code information)) and vital status for those eligible for insurance health services in Ontario, Canada.
CENSUS	Data linked from Statistics Canada to obtain information on demographic characteristics of individuals in Ontario
Ontario Laboratory Information System (OLIS)	Electronic database that contains information on laboratory tests done for patients in Ontario. Data availability begins in 2007.
National Ambulatory Care Reporting System (NACRS)	Contains data (recipient demographics, diagnostic and treatment information) regarding hospital-based and community-based ambulatory care. This dataset also contains information on day surgeries, outpatient and community-based clinics, and emergency departments.
Same Day Surgery (SDS)	Contains demographic, clinical, diagnostic, and procedural data (at the patient level) for all day surgeries performed in Ontario hospitals. This dataset is also built using data from the CIHI.
Ontario Diabetes Database (ODD)	An ICES-derived cohort that uses a validated algorithm to identify Ontarian residents diagnosed with diabetes using data on physician visits and hospitalizations
Ontario Hypertension Database (HYPER)	An ICES-derived cohort that uses a validated algorithm to identify Ontarian residents diagnosed with hypertension using data on physician visits and hospitalizations
Ontario Marginalization Index (ONMARG)	ONMARG contains factor scores and factor quintiles of the Ontario Marginalization Index

	- a census based index to measure social marginalization across Ontario regions. Marginalization are estimated across 4 dimensions: material resources, households and dwellings, age and labour force, and racialized and newcomer populations

Table S2: Data Definitions and Study Outcomes Across Datasets

Variables	Definitions	Dataset	Codes
Demographic Variables			
Age at baseline/index	13-40 years old	RPDB	BDATE
Sex	Male, Female	RPDB	SEX
Rural Residence	Yes or No (Urban)	PSTLYEAR (%getdemo)	rural
Neighbourhood Income Quintile	At index date (Quintiles 1-5; lowest to highest)	PSTLYEAR (%getdemo)	incquint
Cardio-Kidney-Metabolic Risk Factors			
Hypertension	Develops hypertension anytime since index date 0/1 (no/yes) Year of first occurrence	HYPER, CIHI-DAD, OHIP	ICD-10: I10, I11, I12, I13, I15 ICD9 Codes: I10=401X, I11=402X, I12=403X, I13=404X, I15=405X OHIP dx: 401, 402, 403, 404, 405 Gestational records: O10-O16, O21-O95, O98, O99, Z37 ICD9 codes: O10-O16/ O21-O95/O98/O99=641-676, Z37=V270
Diabetes mellitus	Develops diabetes anytime since index date 0/1 (no/yes) Year of first occurrence	ODD	
Hyperlipidemia	Develops hyperlipidemia anytime since index date 0/1 (no/yes) Year of first occurrence	OLIS, CIHI-DAD, OHIP	ICD-10: E780, E782, E784, E785 OHIP dx: 272 ICD9: E780=2720, E782=2722, E784/ E785=2724,
Obesity	Develops obesity anytime since index date 0/1 (no/yes)	CIHI-DAD, NACRS	ICD-10: E66 OHIP dx: 278 ICD9: E66=27800

	Year of first occurrence		
Smoking	Smoking diagnosis anytime since index date 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS	ICD-10: F17, Z72.0 ICD9: F17=2922 Z72.0=V698
Chronic Kidney Disease Indicators			
Albuminuria	Develops albuminuria anytime since index date >3 mg/mmol 0/1 (no/yes) Year of first occurrence	OLIS	Lab value OLIS Observation Code: 32294-1, 30000-4, 14959-1 (Albumin to creatinine ratio (ACR)
eGFR	Develops an eGFR indicative of poor kidney health anytime since index date 2 outpatient eGFR measures >90 days < 720 days apart Below 90 mL/min per 1.73 m2 = indicative of poor kidney health	OLIS	Lab value OLIS Observation Code: 14682-9 (serum creatine levels)
Cardiovascular Outcomes			
Coronary artery disease	Hospitalization or emergency room visit for coronary artery disease since index date 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: I20, I21, I22, I25 (.1), T822, Z955, Z958, Z959, R931 CCI: 1IJ26, 1IJ27, 1IJ50, 1IJ54, 1IJ57, 1IJ76 ICD9 : I20=4111, I21=41010, I22=41012, I23=4230, I24=41181, I25=4292, I25.1=4140,

			T822=99603, Z955/ Z958/V434, R931=7932 CCP: 1IJ50= 4802 1IJ57=4904 1IJ76=481 OHIP dx: 410, 412 OHIP fee: R741, R742, R743, G298, G262, E646, E651, E652, E654, E655, Z434, Z448
Acute coronary syndrome	Hospitalization or emergency room visit for acute coronary syndrome since index date 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: I20, I21, I22-I25 CCI: 1IJ50, 1IJ76 ICD9: I20=4111 I21/ I22=41012 I23=4230 I24=41181 I25=4292 CCP: 1IJ50= 4802 1IJ76=481 OHIP dx: 413, 411-414
Congestive heart failure	**Case definition:** A patient is said to have CHF if s/he had one hospital admission (either from the DAD or from OMHRS) with a CHF diagnosis or an OHIP claim/NACRS ED record with a CHF diagnosis followed within one year by either a second record with a CHF diagnosis from any source 0/1 (no/yes)	DAD, NACRS, OHIP	ICD-10: I500, I501, I509, I255, J81 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR, OHIP FEE: R701, R702, Z429 OHIP dx: 428 ICD9: I500, I501, I509= 428X CCP: 1HP53=4962, 1HP55=4964,

	Year of first occurrence		1HZ53GRFR/ 1HZ53LAFR=4974 1HZ53SYFR=4971
Ischemic stroke	Hospitalization or emergency room visit for ischemic stroke since index date 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341 CCI: 1.ZZ.35.HA-1C ICD9: I62=4321 I630/ I631/ I632=43391 I633=43401 I634=43411 I635/ I638/ I639=4349 I64=436 H341=36235 CCP: 1.ZZ.35.HA-1C =1399 OHIP dx: 435 OHIP fee: A384, K181
Arrhythmia	Hospitalization or emergency room visit for arrythmia since index date 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: I44, I45, I45.6, I45.9, I47, I48, I49, R000, R001, R008, T821, Z450, Z950 CCI: 1HZ53, 1HH59, 1HB53, 1HD55, 1HB55, 1HZ38, 1HZ55 ICD9; I44=426 I45=4264, I45.6=4267, 145.9= 4269 I47/ I48/ I49 =427, R001=42789 R000=7850, R008=7853 T821=99601 Z450=V5331 Z950=V4501 CCP: 1HZ53/1HB53= 4974/4971/4962 1HH59= 4939

			1HD55/1HB55=4986 1HZ38=1379 1HZ55=4983 OHIP dx: 427 OHIP FEE: G178, G179, G249, G261, G259, Z443, Z431, Z437
Venous thromboembolism/pulmonary embolism (VTE/PE)	Hospitalization or emergency room visit for VTE/PE since index date Incident VTE (Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE)) defined as the presence of one diagnosis code AND one imaging code 0/1 (no/yes) Year of first occurrence	CIHI-DAD, NACRS, SDS, OHIP	DVT: - DAD **ICD-10 codes** ("I80.1", "I80.2", "I80.3", I82.2, I82.8, I82.9, O87.1, O87.8, O87.9) AND [OHIP imaging code billed during the hospitalization (“J198” “J498” “J193” “J493” “J202” “J502”) OR a procedure code in the same hospitalization (CCI "3KX30DA" "3KX30DB" "3KX30DC" "3KX30DD" "3KR10VA" "3KR10VC" "3KR10VN" "3KR12VA" "3KX10VA" "3KX10VC" "3KX10VN" "3KX10VX" "3KX12VA")] - NACRS ICD-10 codes ("I80.1", "I80.2", "I80.3", I82.2, I82.8, I82.9, O87.1, O87.8, O87.9, I808, I809, O223, O229) AND [OHIP imaging code billed +/- 7-days (“J198” “J498” “J193” “J493” “J202” “J502”) OR a procedure code in the same visit (CCI "3KX30DA" "3KX30DB" "3KX30DC" "3KX30DD" "3KR10VA" "3KR10VC" "3KR10VN" "3KR12VA" "3KX10VA" "3KX10VC" "3KX10VN" "3KX10VX" "3KX12VA")] - [OHIP ICD-9 code (‘451’ ‘671’) AND location in (‘O’ ‘H’ ‘L’ ‘P’)] AND OHIP

			imaging code billed +/- 7-days (“J198” “J498” “J193” “J493” “J202” “J502”) PE: -DAD icd10 ("I26", “O882”) AND [OHIP imaging code billed during the hospitalization (J659, J660, J859, J860, X406, X407, X125) **OR** a procedure code in the same hospitalization (**CCI** "3IM10VC" "3IM10VX" "3IM10VY" "3IM12VA" "3GT70CA" "3GT70CC" "3GT70CE" "3GT70KC" "3GT70KD" '3GT70KE" "3JY10VA" "3JY10VC" "3JY10VN" "3JY10VX" "3JY12VA" "3JY20WC" "3JY20WE" "3GT20WC" "3GT20WE") - NACRS **ICD-10 codes** ("I26", “O882”)) AND [OHIP imaging code billed within 7-days (J659, J660, J859, J860, X406, X407, X125 OR a procedure code in the same visit (**CCI** "3IM10VC" "3IM10VX" "3IM10VY" "3IM12VA" "3GT70CA" "3GT70CC" "3GT70CE" "3GT70KC" "3GT70KD" '3GT70KE" "3JY10VA" "3JY10VC" "3JY10VN" "3JY10VX" "3JY12VA" "3JY20WC" "3JY20WE" "3GT20WC" "3GT20WE")] -DAD icd10 ("I26", “O882”) AND [OHIP imaging code billed during the hospitalization (J659, J660, J859, J860, X406, X407, X125) **OR** a

			procedure code in the same hospitalization (**CCI** "3IM10VC" "3IM10VX" "3IM10VY" "3IM12VA" "3GT70CA" "3GT70CC" "3GT70CE" "3GT70KC" "3GT70KD" '3GT70KE" "3JY10VA" "3JY10VC" "3JY10VN" "3JY10VX" "3JY12VA" "3JY20WC" "3JY20WE" "3GT20WC" "3GT20WE") - NACRS **ICD-10 codes** ("I26", "O882")) AND [OHIP imaging code billed within 7-days (J659, J660, J859, J860, X406, X407, X125 OR a procedure code in the same visit (**CCI** "3IM10VC" "3IM10VX" "3IM10VY" "3IM12VA" "3GT70CA" "3GT70CC" "3GT70CE" "3GT70KC" "3GT70KD" '3GT70KE" "3JY10VA" "3JY10VC" "3JY10VN" "3JY10VX" "3JY12VA" "3JY20WC" "3JY20WE" "3GT20WC" "3GT20WE")] ICD9: I80.1=45111 I80.2=45119 I80.3= 4512, I82.2= 4532 I82.8= 4538 I82.9= 4539, O87.1= 67142 O87.8= 67182 O87.9=67192 I808=45189 I809=4519 O223= 67131 O229=67191 I26=4150

			O882=67321 CCP 3KX30DA /3KX30DB/ 3KX30DC/ 3KX30DD=0289 3KR10VA/3KR10VC/3KR 10VN=5089 3KX10VA/3KX10VC/3KX 10VN/3KX10VX=5080 3IM10VC/3IM10VX/3IM1 0VY=5083, 3GT70CA/3GT70CC/3GT7 0CE/3GT70KC/3GT70KD/ 3GT70KE=0615 3JY10VC/3JY10VN/3JY10 VX=5084 3GT20WC/3GT20WE=022 1
Comorbidities			
Malignancy	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: C00-C97 OHIP dx: 140-160, 161-165, 170-175, 179, 180-208, 230-234 OHIP fee: R105, R107, R108, R109, R111, R117, R913, R914, E525, E546, E505, Z139, Z141, S645, S646, S647, S648, S649, S650, S651, S652, S653, S654, S655, Z712, S149, S154, S156, S157, S158, S160, S162, S164, S165, S166, S167, S168, S169, S170, S171, S172, S173, S176,S180, S185, S188, S213, S214, S215, S217, S312, Z750, S249, Z754, Z784, Z785, M142, M143, M144, M145, M111, M135, M137, Z328, Z329, Z330, Z331, Z332, Z333, Z335, Z337, Z339, Z341, Z347, Z348, Z357, R912, R913,

			S704, S705, S710, S714, S738, S744, S745, S750, S754, S757, S758, S759, S762, S763, S764, S765, S766, S767, S776, S781, S782, S810, Z553, Z563, Z583, Z720, Z723, Z729, Z730, Z731, Z735, Z766, Z769, G281, G339, G345, G359, G381, G382, G388, Z511, Z512 CCI: 1YM89, 1YM90, 1YM91, 1YM92, 1QT91, 1NM87, 1NM89, 1NM91, 1NQ87, 1NQ89, 1NQ90, 1RM89, 1RM91 2GX71DA, 1ME89DA, 2GV70LA, 2GX71LA, 2GM71LA, 1ME89LA, 2GV71LA, 2MB71LA, 2GV70DA, 2GT71DA, 2GY70LA, 2GY70DA, 2GT71LA, 1ME87DA, 1MF87LA, 1ME87LA, 2GW71LA, 2GT70LA, 2GW70LA, 2MF71LA, 2GW71DA, 2GW70DA, 2ME71LA, 2ME71DA, 1GM59BAAG, 1GM59BAGX, 1GT52DA, 1GT59DAAG, 1GT59DAGX, 1GV52DA, 1GV52DATS, 1GV52HA, 1GV52HAHE, 1GV52HATK, 1GV52LA, 1GV52LATS, 1GV52LAXXE, 1GV59DAGX, 1GV59DAZ9, 1GV59HAZ9, 1GV59LAGX, 1GV87DA, 1GV87LA, 1HA52DA, 1HA52HA, 1HA52HATS, 1HA52QA, 1HA52QB, 1GR87QB, 1GR87DA,

			1GR87NW, 1GR89QB, 1GR91QB, 1GR89DA, 1GR89NW, 1GT87QB, 1GR91NWXXF, 1GT87NW, 1GT87DA, 1GT89QB, 1GT91QB, 1GT89NW, 1GT89DA, 1GT91NW
Non-kidney solid organ transplant	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: Z94 (all except .0) (so Z941 Z942 Z943 Z944 Z945 Z946 Z947 Z948 Z949) OHIP fee: S294, S295, E765, G254, S265, S266, M155, M156, S308, R874, R870 CCI: 1OA85, 1HZ85, 1GT85
Congenital heart disease	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: **Q20-Q24 (more heart specific);** Q20-Q28 (circulatory) OHIP dx: 746, 747
Cardiac surgery:	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	OHIP fee: R765, R740, R711, R709, R710, R706, R712, R713, R714 ,Z743, Z780, R718, R716, R715, R717, R759, R742, R743, R763, R762, Z744, Z781, R872, R747, R741 , R746, R920, Z436, Z788, R753, R761, Z429, R751, Z444, Z435, R857, R755, R754, R870, Z428, Z465, Z466, R749, R748, Z415, Z759, Z433, Z412, Z751, Z782, Z445, R758, R756, R757, Z401, Z414, R750, R702, R704, R703, R705 , R701 R700, R927, R721, R921, R770, R929, R924, R923, R926, R768, R769, R928, R922, R722, R723, R720, R925, R771

			CCI: 1.IJ.76.^^, 1.HS.^^, 1.HT.^^, 1.HU.^^, 1.HV.^^, 1.HW.^^ (1IJ26, 1IJ50, 1IJ55, 1IJ57, 1IJ76, 1IJ80)
Chronic liver disease	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10 codes: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K72, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77, I864 I982 K711, Z944 OHIP dx: 571, 573, 70 (070) OHIP fee: Z551, Z554
Sickle cell disease	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: D57 OHIP dx: 282
Lung disease	2 year look back from index for history of 1) hospitalization and/or 2) physician billings 0/1 (no/yes)	CIHI-DAD, NACRS, SDS, OHIP	ICD-10: I272, I278, I279, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99 OHIP dx: 491, 492, 493, 494, 496, 501, 502, 511, 512, 515, 518, 519 OHIP fee: J889, J689
Healthcare Utilization			
Primary care visit	Frequency of physician billing claims for primary care visits during follow-up Primary care (FP/GP visits, non-emergency visits etc)	OHIP	OHIP fee codes <u>Family medicine consultation</u>: A005, A911, A912, A905, A003, A900, A933 <u>Repeated consultation:</u>

	0/1 (no/yes)		A006, A004 <u>Periodic health visit:</u> K131, K132 <u>Non-emergency inpatient services:</u> C005, C911, C912, C905, C006, C003, C004 <u>Subsequent visits</u>: C002, C007, C009
Referral to a specialist	Frequency of physician billing claims for specialist visits during follow-up Specialist visits (ex. cardiologist, endocrinologist, nephrologist etc.) Flag (0/1) for each type of specialist	OHIP	OHIP fee codes **Cardiologist** <u>Cardiology consultation:</u> A605, A765, A600, A675, A606, A603, A604, A601, A608 <u>Cardiology non-emergency visit</u>: C605, C765, C600, C675, C606, C603, C604, C601 <u>Cardiology subsequent visits:</u> C602, C607, C609 **Endocrinologist** <u>Endocrinology consultation</u>: A155, A765, A150, A255, A156, A153, A154, A151, A158 **Endocrinology non-emergency visit**: C155, C765, C150, C255, C156, C153, C154, C151 <u>Endocrinology subsequent visits:</u> C152, C157, C159 **Nephrologist** <u>Nephrology consultation:</u> A165, A765, A160, A865, A166, A163, A164, A161, A168

			Non-emergency nephrology visit: C165, C765, C160, C865, C166, C163, C164, C161 Nephrology subsequent visits: C162, C167, C169
Other			
Death	All-cause mortality, following index date 0/1 (no/yes) Dth year	RPDB	DTH

Analysis of Obesity Trends

The total period prevalence of obesity amongst the cohort stood at 5.61% (Table S3). The age-sex standardized incidence rate of obesity in the adolescent and young adult population of Ontario steadily declined from 2006 but saw a significant increase after 2020, in the post-pandemic era (Figure S1, A). Compared to 2006-2009, the incidence rate decreased by 18% (IRR 0.82, 95% CI 0.78-0.87) by 2015-2019 but was 12% lower in 2020-2023 compared to what it was originally (IRR 0.88, 95% CI 0.83-0.93) (Table S3). Similar trends were observed in crude incidence rates when stratified by age group and by sex (Figure S1, B-C). Those who were 13-18 years olds saw the largest average annual percent decrease (APC -2.2%, 95% CI -2.5-1.9%; Figure S1, E) in incidence and by 2020-2023 had the largest decrease in incidence compared to other age groups (IRR 0.71, 95% CI 0.62-0.80) (Table S4; Figure S1, D).

Table S3. Period Prevalence, New Cases per Era, and Adjusted Incidence Rate Ratios by Era for Obesity in Young People (13-40 years old) in Ontario

Result	2006-2023	2006-2009	2010-2014	2015-2019	2020-2023
Period Prevalence and New Cases by Era					
Total Period Prevalence %, (n)	5.61, (318451)	-	-	-	-
New Cases	-	81789	80541	81359	74762
Adjusted Incidence Rate Ratio by Era					
IRR (95% CI) (Era v.s. 2006-2009)	-	-	0.82 (0.78-0.87)	0.82 (0.78-0.87)	0.88 (0.83-0.93)

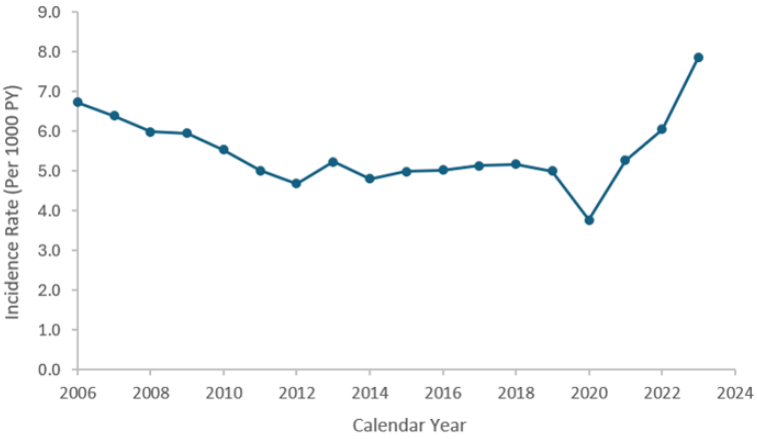
*Adjusted for age, sex, rural residence, and income quintile

Table S4. Adjusted Incidence Rate Ratios (Era v.s. 2006-2009) by Age Group and Sex and Annual Percent Change in Incidence for Obesity Among Young People in Ontario

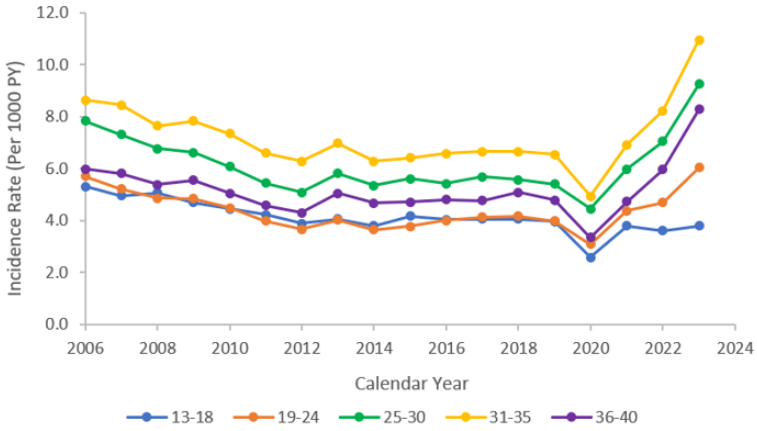
Result	Age Group					Sex	
	13-18	19-25	25-30	31-35	36-40	Male	Female
Adjusted Incidence Rate Ratios by Age Group and Sex							
IRR (95% CI) (2010-2014)	0.84 (0.75-0.95)	0.82 (0.73-0.93)	0.79 (0.70-0.89)	0.82 (0.73-0.92)	0.85 (0.75-0.96)	0.85 (0.81-0.89)	0.79 (0.75-0.83)
IRR (95% CI) (2015-2019)	0.84 (0.74-0.94)	0.82 (0.72-0.93)	0.80 (0.71-0.90)	0.80 (0.71-0.90)	0.85 (0.76-0.96)	0.85 (0.81-0.89)	0.79 (0.75-0.84)
IRR (95% CI) (2020-2023)	0.71 (0.62-0.80)	0.91 (0.80-1.02)	0.91 (0.81-1.03)	0.92 (0.82-1.04)	0.95 (0.85-1.07)	0.79 (0.75-0.82)	0.96 (0.91-1.01)
Average Annual Percent Change (%) in Incidence by Age Group							
APC (95% CI)	-2.2 (-2.5, -1.9)	-0.4 (-0.9, 0.0)	-0.4 (-0.8, 0.1)	-0.4 (-0.8, 0.1)	0.0 (-0.4, 0.5)	-	-

*Adjusted for age (sex stratified models), sex (for age models), rural residence, and income quintile

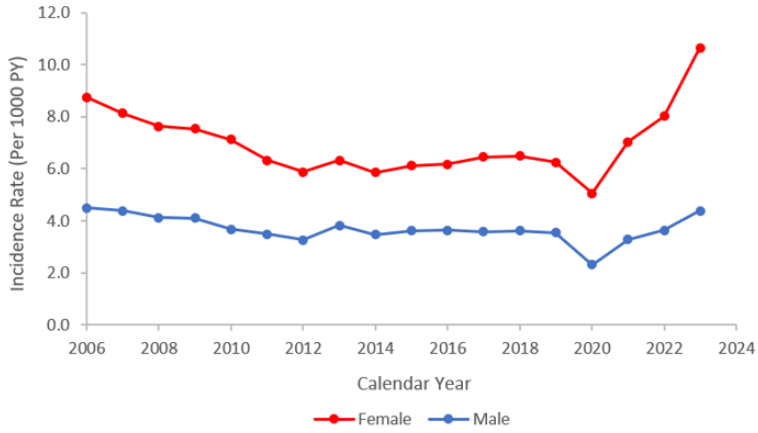
A. Age-Sex Standardized Incidence Rate (2006-2023)



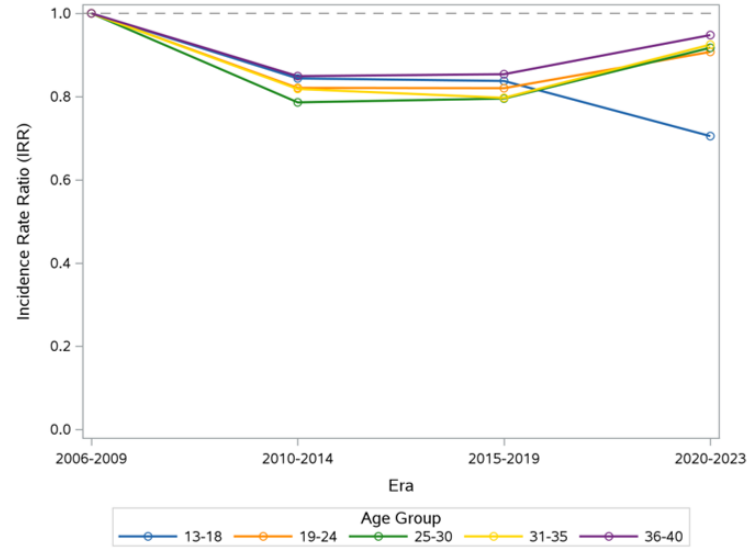
B. Incidence Rate by Age Group (2006-2023)



C. Incidence Rate by Sex (2006-2023)



D. Adjusted Incidence Rate Ratio (IRR) by Age Group



E. Annual Percent Change in Incidence by Age Group

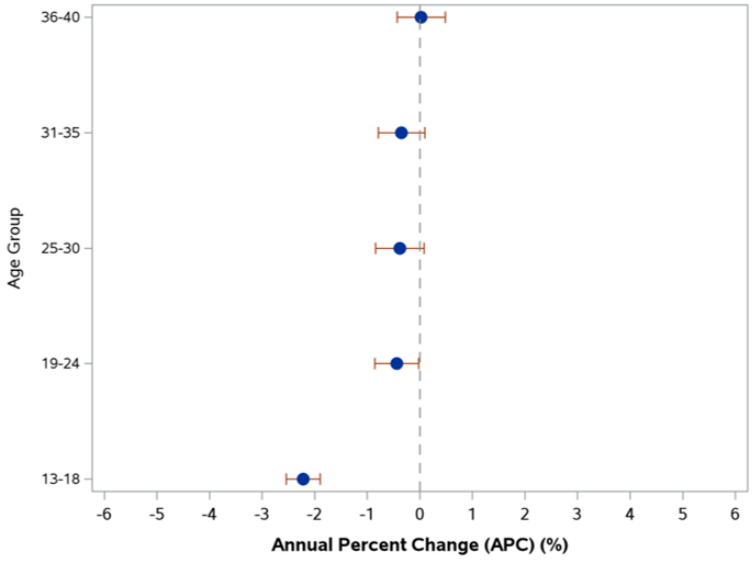


Figure S1. Results of the Analysis for Obesity in Young Ontarians (13-40 Years Old)

Additional CKD Analysis

Table S5. Adjusted[1] Incidence Rate Ratios (95% CI) by Era for CKD Indicators in Young People (13-40 years old) in Ontario

Result	2015-2019	2020-2023
ACR > 3 mg/mmol	1.29 (1.17-1.44)	2.02 (1.80-2.27)
*eGFR < 60 min/mL/1.73 m^2	1.48 (1.30-1.70)	1.73 (1.52-1.98)

*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other

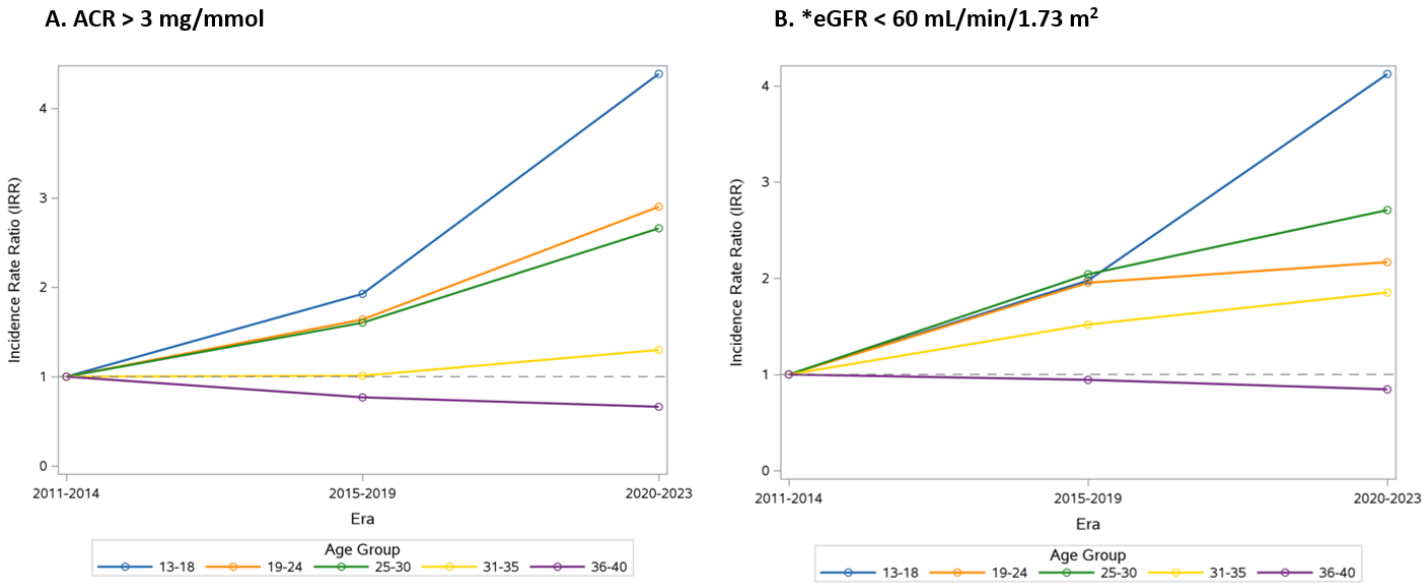
[1]Adjusted for age, sex, rural residence, income quintile, and total lab tests per year

Table S6. Adjusted[1] IRRs (v.s. Reference Era 2011-2014) and APCs (95% CIs) by Age Group and Sex for CKD Indicators

CKD Indicator	Age Group					Sex	
	13-18	19-25	25-30	31-35	36-40	Male	Female
IRR (95% CI) 2015-2019							
ACR > 3 mg/mmol	1.93 (1.73-2.15)	1.64 (1.47-1.83)	1.60 (1.44-1.79)	1.01 (0.91-1.13)	0.77 (0.69-0.86)	1.23 (1.06-1.43)	1.51 (1.31-1.73)
*eGFR < 60 min/mL/1.73 m2	1.98 (1.47-2.66)	1.95 (1.60-2.39)	2.04 (1.71-2.44)	1.52 (1.30-1.77)	0.94 (0.82-1.08)	1.47 (1.15-1.88)	1.26 (1.02-1.56)
IRR (95% CI) 2020-2023							
ACR > 3 mg/mmol	4.39 (3.93-4.91)	2.90 (2.59-3.25)	2.66 (2.37-2.99)	1.30 (1.16-1.45)	0.66 (0.59-0.74)	1.86 (1.59-2.18)	2.47 (2.12-2.88)
*eGFR < 60 min/mL/1.73 m2	4.12 (3.06-5.55)	2.17 (1.77-2.66)	2.71 (2.27-3.23)	1.85 (1.59-2.15)	0.84 (0.74-0.97)	1.70 (1.33-2.16)	1.50 (1.23-1.84)
Average Annual Percent Change (95% CI)							
ACR > 3 mg/mmol	13.7 (12.4, 15.0)	9.2 (8.1, 10.4)	9.0 (7.8, 10.2)	0.8 (-0.3, 1.9)	-6.5 (-7.5, -5.6)	-	-
*eGFR < 60 min/mL/1.73 m2	17.3 (12.1, 22.8)	6.4 (3.2, 9.7)	11.4 (8.5, 14.4)	7.3 (4.9, 9.8)	-3.9 (-5.9, -1.7)	-	-

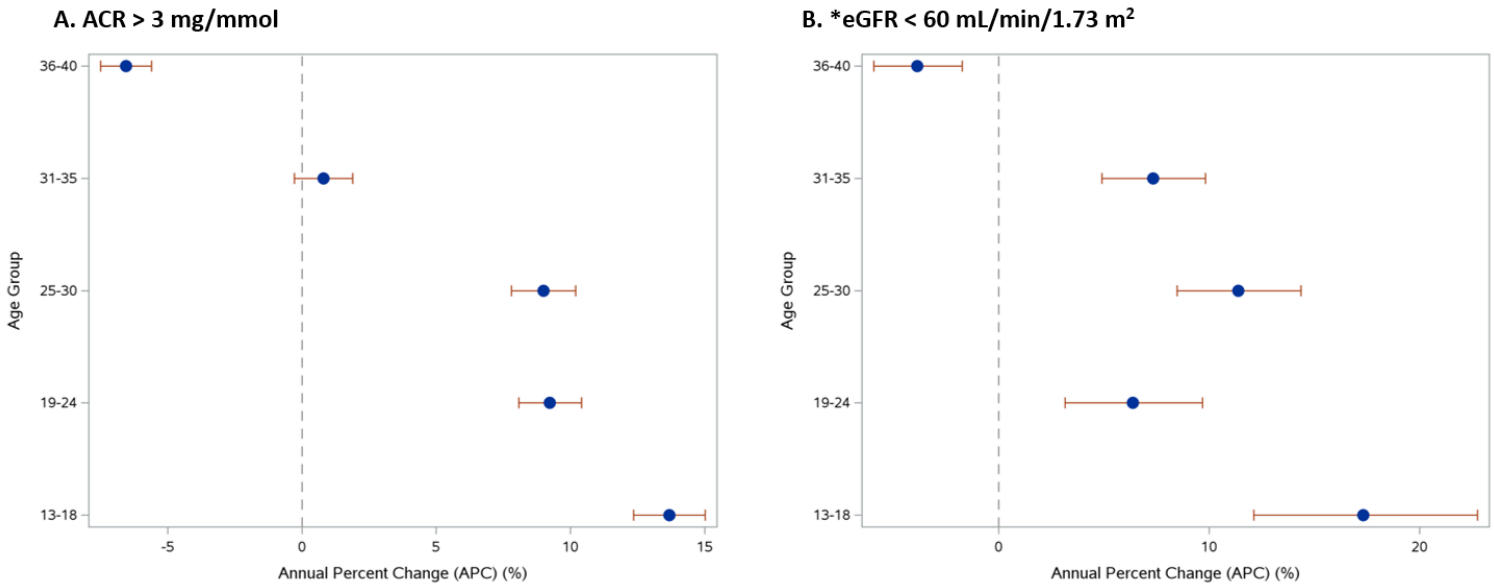
*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other

[1]Adjusted for age (for sex stratified models), sex (for age models), rural residence, income quintile, and total lab tests per year



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.
[1]Adjusted for sex, rural residence, income quintile, and total lab tests per year

Figure S2. Adjusted[1] Incidence Rate Ratios (IRRs) (95% CI) Stratified by Age Group for CKD Indicators



*CKD was defined as 2 eGFR measures < 60 that were taken 90 to 720 days within each other.
[1]Adjusted for sex, rural residence, income quintile, and total lab tests per year

Figure S3. Forest Plot of Annual Percent Change (APC, %) in Incidence by Age Group for CKD Indicators