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Incident chronic kidney disease among Canadian immigrants: a population-based cohort study

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ABSTRACT

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

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

Results The study cohort included 10 440 210 Ontario residents, consisting of 22% immigrants (n=2 253 360) and 78% (n=8 186 850) non-immigrants. The mean (SD) age and eGFR were 45 (17) years and 102 (16) mL/min/1.73 m^2, respectively, and 54% of individuals were female. A total of 117 028 immigrants (5%, 7 events per 1000 person-years) and 984 277 non-immigrants (12%, 16 events per 1000 person-years) developed incident CKD during follow-up. Immigrants experienced a 20% lower risk for incident CKD compared with non-immigrants (adjusted HR 0.80, 95% CI 0.80 to 0.81). Consistent findings were seen for refugee and non-refugee immigrants, immigrants with remote (1985–2004) and recent (2005–2020) landing dates, and immigrants from different world regions. Results were similar on re-defining incident CKD as two outpatient eGFR measurements <60 mL/min/1.73 m^2 at least 90 days apart, treating death as a competing risk, and adjusting for baseline albuminuria.

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

WHAT IS ALREADY KNOWN ON THIS TOPIC

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

WHAT THIS STUDY ADDS

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

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

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

INTRODUCTION

Chronic kidney disease (CKD) is a major global health issue, affecting over 800 million people worldwide.[1] In Canada, it is estimated that CKD affects one in 10 individuals.[2] CKD is defined either by evidence of kidney damage, indicated by albuminuria, or more commonly by a reduction in kidney function, indicated by a reduction in glomerular filtration rate (GFR). The standard estimated GFR (eGFR)

cut-off adopted to define CKD is <60 mL/min/1.73 m^2 as this represents a decline in kidney function to approximately half of what is seen in healthy young adults and associates with increased morbidity and mortality at the population level.[3 4] CKD predisposes to a host of health complications including hypertension, cardiovascular disease, anaemia, kidney failure, death and reduced quality of life.[5] Therefore, early detection and treatment of CKD is imperative to slow its progression and prevent adverse CKD-related outcomes.

Social determinants of health (ie, non-medical factors that influence health outcomes) are increasingly recognised to be strongly linked to both CKD incidence and outcomes.[6] For instance, factors such as race/ethnicity, unemployment, poverty and low education, are associated with poor kidney health.[7–18] An understudied social determinant of health in relation to kidney disease is immigrant status. Canada takes great pride in being an 'immigrant friendly' country, becoming a major destination for immigrants globally. Universal healthcare coverage begins shortly after an immigrant arrives in Canada. Current immigration rates in Canada are among the highest for any country in the world and continue to rise, translating into approximately one quarter of the Canadian population being comprised of foreign-born immigrants.[19]

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

METHODS

Study design and setting

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

Data sources

We ascertained baseline characteristics and outcome data from de-identified, linked databases housed at ICES. Demographic and vital status information was obtained from the Ontario Registered Persons Database. Immigrant-specific information was obtained from the Immigration, Refugee and Citizenship Canada (IRCC) Permanent Resident Database.[28] Diagnostic and procedural information from all hospitalisations were determined using the Canadian Institute for Health Information Discharge Abstract Database. Diagnostic information from emergency room and day surgery visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan database, which contains all health claims for inpatient and outpatient physician services. Laboratory information is contained in the Ontario Laboratory Information System which captures laboratory tests for all patients in Ontario. Definitions for patient characteristics and clinical variables can be found in online supplemental table 2. These datasets were linked using unique encoded identifiers and analysed at ICES. The databases were complete for all variables used except for rural residence, neighbourhood income quintile and immigrant world region of origin, which were missing in <0.5% of individuals. The only reason for lost follow-up was emigration from the province which occurs in<0.5% of Ontario residents annually.[29]

Cohort definition

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

Exposure

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

non-permanent resident) immigrants to Canada were not captured within the ICES datasets and therefore not included in the study.

Outcomes

The primary outcome was incident CKD, defined as an outpatient eGFR <60 mL/min/1.73 m^2. Inpatient or emergency room eGFR measurements were not included so as to minimise the risk of capturing acute kidney injury (AKI) events. A single outpatient eGFR measurement has previously been shown to provide an accurate estimate of kidney function in a similar ICES-based cohort[31] and external cohorts.[32 33] We further assessed the outcome of incident CKD in alignment with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as two outpatient eGFR measurements <60 mL/min/1.73 m^2 at least 90 days apart.[34]

Statistical analysis

Baseline characteristics were ascertained for immigrants and non-immigrants. Continuous variables were reported as mean (SD), while categorical variables were reported as number (%). Crude CKD incidence rates (events/1000 person-years) were calculated for immigrants and non-immigrants. Multivariable Cox proportional hazards modelling was used to measure the association between immigrant status and incident CKD. Models were adjusted for the following variables selected a priori based on clinical knowledge and previous literature: age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighbourhood income quintile and prior history of cardiovascular disease (composite of myocardial infarction, ischaemic stroke, congestive heart failure and coronary artery bypass graft surgery).[5] Additional multivariable Cox models were used to compare the risk for incident CKD between: (A) refugee versus non-refugee immigrants, (B) immigrants with remote (1985–2004) versus recent (2005–2020) landing dates and (C) immigrants coming to Canada from different regions of the world. We conducted all analyses using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA). 95% CIs that did not overlap with 1.0 and two-sided p values<0.05 were treated as statistically significant.

Additional analyses

Additional analyses included: (A) re-defining the incident CKD outcome as two outpatient eGFR measurements <60 mL/min/1.73 m^2 at least 90 days apart as per KDIGO guidelines,[34] (B) using Fine-Gray subdistribution hazard models accounting for the competing risk of death and (C) restricting the study cohort to those with a urine albumin-to-creatinine ratio (UACR) within 1 year

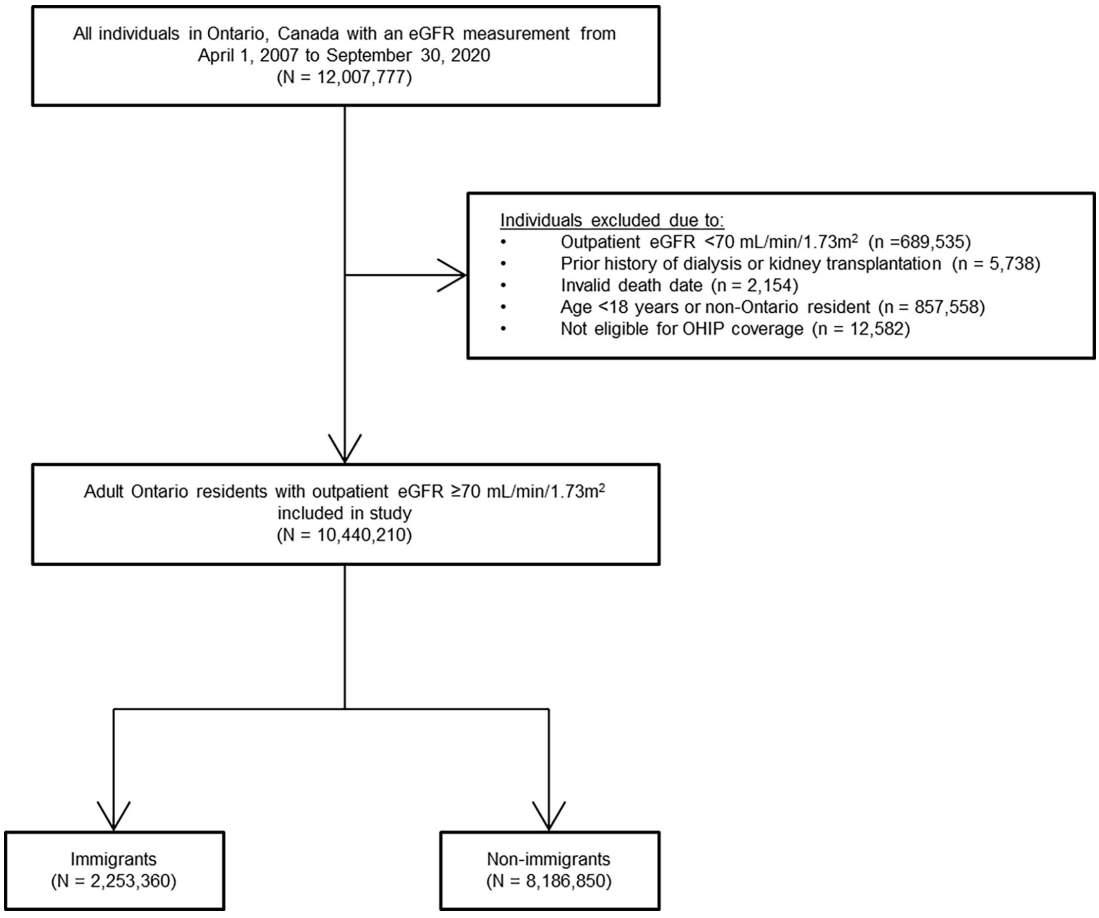

Figure 1 Study flowchart. eGFR, estimated glomerular filtration rate; OHIP, Ontario Health Insurance Plan.

Table 1 Baseline characteristics of the study cohort

Characteristic	Overall	Immigrants	Non-immigrants
N (%)	10 440 210	2 253 360 (22)	8 186 850 (78)
Age, years, mean (SD)	45 (17)	41 (14)	47 (18)
Sex, N (%)			
Female	5 589 599 (54)	1 224 262 (54)	4 365 337 (53)
Male	4 850 611 (46)	1 029 098 (46)	3 821 513 (47)
Baseline eGFR, mL/min/1.73 m^2, mean (SD)	102 (16)	107 (15)	101 (16)
Neighbourhood income quintile, N (%)*			
Quintile 1 (lowest)	2 053 854 (20)	627 826 (28)	1 426 028 (17)
Quintile 2	2 082 562 (20)	509 345 (23)	1 573 217 (19)
Quintile 3	2 084 203 (20)	452 378 (20)	1 631 825 (20)
Quintile 4	2 131 199 (20)	392 621 (17)	1 738 578 (21)
Quintile 5 (highest)	2 054 481 (20)	266 216 (12)	1 788 265 (22)
Rural residence, N (%)†	1 056 347 (10)	22 855 (1)	1 033 492 (13)
Comorbidities			
Arrhythmia, N (%)	82 672 (1)	6616 (0)	76 056 (1)
Atrial fibrillation, N (%)	83 937 (1)	4546 (0)	79 391 (1)
CABG, N (%)	31 022 (0)	2755 (0)	28 267 (0)
Chronic liver disease, N (%)	302 097 (3)	85 272 (4)	216 825 (3)
Congestive heart failure, N (%)	149 500 (1)	10 036 (0)	139 464 (2)
COPD, N (%)	652 206 (6)	44 495 (2)	607 711 (7)
Coronary artery disease, N (%)	593 164 (6)	67 956 (3)	525 208 (6)
Diabetes mellitus, N (%)	903 071 (9)	162 089 (7)	740 982 (9)
Hypertension, N (%)	2 368 505 (23)	337 779 (15)	2 030 726 (25)
Ischaemic stroke, N (%)	45 886 (0)	3904 (0)	41 982 (1)
Major cancer, N (%)	382 878 (4)	39 324 (2)	343 554 (4)
Myocardial infarction, N (%)	84 734 (1)	7358 (0)	77 376 (1)

*Neighborhood income quintile missing in 33 911 individuals (0.3% of cohort).
†Rural defined as residing in a location with population <10 000, missing in 11 671 individuals (0.1% of cohort).
CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

of index and adjusting for UACR within the regression models.

RESULTS

Baseline characteristics

From a total of 12 007 777 Ontario residents with an eGFR measurement within the accrual period, 10 440 210 met our inclusion criteria (figure 1). The study cohort consisted of 2 253 360 (22%) immigrants and 8 186 850 (78%) non-immigrants (table 1). The mean (SD) age of the cohort was 45 (17) years with immigrants being generally younger (mean (SD) age 41 (14) years; median (IQR) age 39 (30–50) years) than non-immigrants (mean (SD) age 47 (18) years; median (IQR) age 47 (32–59) years). Females made up 54% of the cohort which was similar among both immigrants and non-immigrants. The mean (SD) baseline eGFR of the cohort was 102 mL/min/1.73 m^2 with immigrants having slightly higher values. Immigrants generally lived in neighbourhoods with lower income levels, less commonly resided in rural areas and had fewer comorbidities. Immigrant-specific characteristics are displayed in table 2. Refugees represented 17% of the immigrant population. Immigrants came from all regions around the world with approximately half coming from Asia.

Incident chronic kidney disease by immigrant status

A total of 117 028 immigrants (5%) and 984 277 non-immigrants (12%) developed incident CKD over the follow-up period. This translated into a crude incidence rate seven events/1000 person-years for immigrants as compared with 16 events/1000 person-years for non-immigrants. In the multivariable Cox regression models, immigrants experienced a 20% lower risk for incident CKD compared with non-immigrants (adjusted HR (aHR) 0.80, 95% CI 0.80 to 0.81)—the

Table 2 Immigrant-specificcharacteristics

Characteristic	
Year of landing, N (%)	
1985–1989	186 525 (8)
1990–1994	350 155 (16)
1995–1999	321 800 (14)
2000–2004	402 574 (18)
2005–2009	368 099 (16)
2010–2014	318 394 (14)
2015–2020	305 813 (14)
World region of origin, N (%)*	
Africa	161 179 (7)
Asia	1 096 777 (49)
Europe	409 750 (18)
Middle East	198 349 (9)
North America	220 173 (10)
South America	114 297 (5)
Stateless	52 593 (2)
Immigrant type	
Refugee, N (%)	373 387 (17)
Non-refugee, N (%)	1 879 973 (83)

*World region of origin missing for 242 individuals (0.01% of immigrants).

adjusted cumulative incidence curves are displayed in figure 2. Both refugee (aHR 0.87; 95% CI 0.86 to 0.89) and non-refugee immigrants (aHR 0.79; 95% CI 0.79 to 0.80) experienced a lower risk for incident CKD compared with non-immigrants. Immigrants with remote (1985–2004; aHR 0.78; 95% CI 0.78 to 0.79) and recent (2005–2020; aHR 0.87; 95% CI 0.86 to 0.88) landing dates experienced a lower risk for incident CKD compared with non-immigrants.

Incident chronic kidney disease among immigrants by world region

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

Additional analyses

Results were similar on re-defining incident CKD as two outpatient eGFR measurements <60 mL/min/1.73 m^2 at least 90 days apart (online supplemental table 3), treating death as a competing risk (online supplemental table 4) and

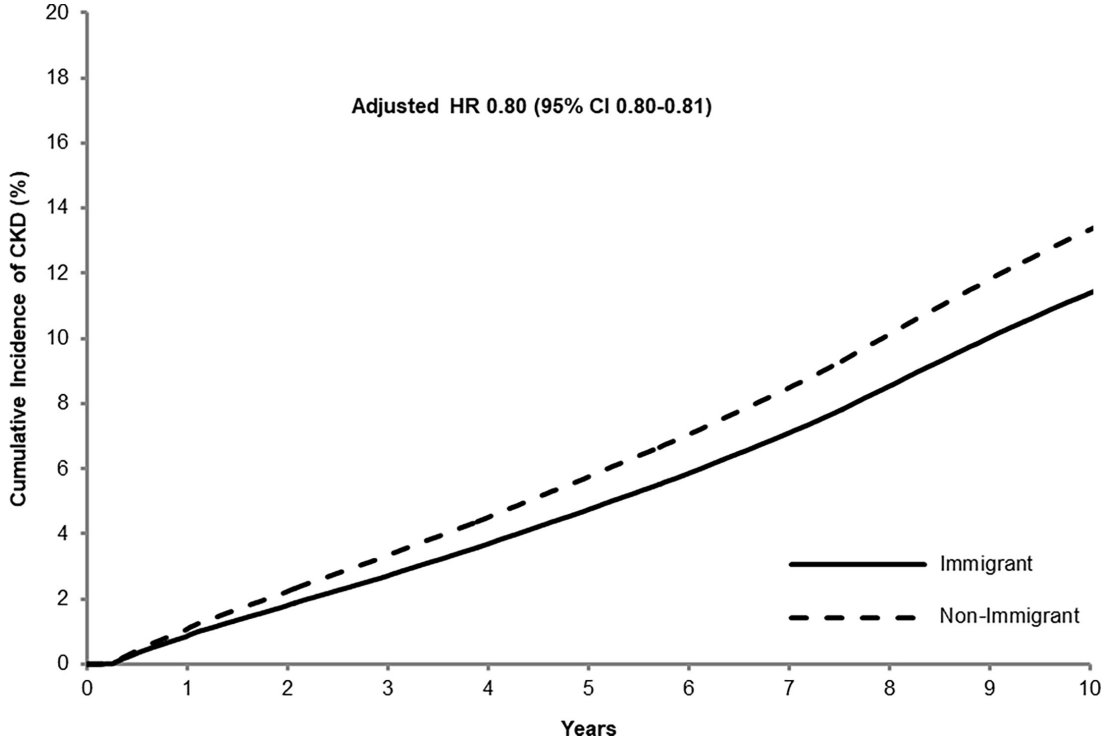

Figure 2 Adjusted cumulative incidence curves for chronic kidney disease among immigrants vesus non-immigrants. Chronic kidney disease defined as outpatient eGFR <60 mL/min/1.73 m^2. Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighbourhood income quintile and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischaemic stroke, congestive heart failure and coronary artery bypass graft surgery) determined at index. CKD, chronic kidney disease.

adjusting for baseline UACR in the subset of individuals with UACR measurements within 1 year of index (n=5831 immigrants, n=25 461 non-immigrants) (online supplemental table 5).

DISCUSSION

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

The seemingly protective effect of being an immigrant on CKD incidence may be explained by the 'healthy immigrant effect'. This term refers to a phenomenon whereby immigrants have a health advantage over their domestic-born counterparts.[21–25] For example, a systematic review found that adult immigrants had similar or better health compared with Canadian-born adults, particularly in regard to chronic health conditions.[35] This may relate to differences in health-related behaviours among immigrants such as healthier diet, increased physical activity, lower alcohol consumption and reduced smoking rates.[23 24 36–38] The 'healthy immigrant effect' may also be explained by the immigration selection process itself with healthier individuals being more likely to immigrate and less healthy individuals being more likely to remain in their country of origin.[39 40] Specific to the Canadian immigration process, a point system is employed based on human capital which favours individuals with higher education and language skills for the economic class of immigrants that will contribute to successful living post-migration.[35 41] Notably, these social factors are known to correlate with better health, including kidney health.[15 16 18] Further, the medical screening tests required during the immigration process may promote systematic selection. While this 'healthy immigrant effect' has been shown to diminish over time in relation to other chronic health conditions, due to stressors in adjusting to a new living environment and adoption of unhealthy behaviours,[38 42 43] we found a sustained effect in relation to CKD incidence even among immigrants with remote landing dates.

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

An interesting finding relates to the differential incident CKD risk based on world region. There was no difference in incident CKD risk for immigrants from North America, individuals who may be most similar to Canadian-born adults in regard to not only geography but also health-related behaviours. Immigrants from all other regions experienced a lower incident CKD risk. However, the absolute effect size was minimal for immigrants from Africa which may relate to predisposing CKD risk factors common among individuals of African descent such as APOL1 variants.[46]

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

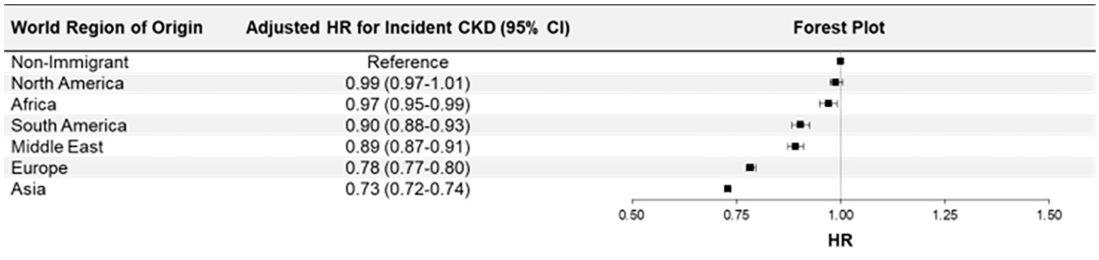

Figure 3 Risk of incident chronic kidney disease among immigrants by world region of origin. Chronic kidney disease defined as outpatient eGFR <60 mL/min/1.73 m^2. Models adjusted for age, sex, diabetes mellitus, hypertension, baseline eGFR, rural residence, neighbourhood income quintile and prior history of cardiovascular disease (defined as a composite of myocardial infarction, ischaemic stroke, congestive heart failure and coronary artery bypass graft surgery). CKD, chronic kidney disease.

Our results must be interpreted within the context of the study design. First, this study was observational; therefore, we were able to identify association but not causation. However, our analytic models adjusted for numerous potential confounders that should reduce observed confounding though we acknowledge that unobserved confounding may still occur. Second, our primary analysis defined incident CKD as a single outpatient eGFR measurement <60 mL/min/1.73 m^2 which may lead to some degree of misclassification (eg, outpatient AKI). However, our results were consistent on re-defining incident CKD as two outpatient eGFR measures <60 mL/min/1.73 m^2 at least 90 days apart, consistent with KDIGO guidelines.[34] Third, CKD is defined not only by a reduction in kidney function (eGFR) but also by kidney damage (albuminuria). The results from a sensitivity analysis adjusting for UACR among the subset of individuals with available measures within 1 year of index were consistent. Fourth, medication data in Ontario are available only for individuals ≥65 years of age. As the vast majority of our cohort was below this age cut-off, we were unable to adjust for medications that may impact kidney function (eg, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors). Fifth, as the IRCC database captures all immigrants to Canada from 1985 onwards, we were unable to distinguish between individuals who were born in Canada and long-term residents who immigrated to Canada prior to 1985. This misclassification may have attenuated the magnitude of the associations between immigrant status and incident CKD risk. Sixth, as immigrants who are non-citizens or non-permanent residents to Canada are not captured within the ICES datasets, we have no data on this population, and the results from this study may not generalise to these individuals. The characteristics of this population may be quite different, and their more limited access to healthcare within Canada may further influence their long-term health outcomes. Though this population is generally small within Canada,[47] this non-citizen (or non-permanent resident) immigrant population is an important one for future research. Finally, as the outcome data relied on outpatient eGFR measurements captured as part of real-world medical care rather than at prespecified time intervals, this likely contributed to an element of interval censoring which may have attenuated the measured associations.

CONCLUSION

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

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Contributors I-EO, MMS, PT and GLH conceptualised the study. I-EO, CY and MT conducted data management and statistical analysis. MMS, AA, PT, IM, GAK and GLH provided overall supervision of the manuscript. I-EO and GLH drafted the first manuscript. All authors provided critical revision and editing of the manuscript. All authors read and approved the final manuscript. GLH is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The dataset from this study is held securely in coded form at Institute for Clinical Evaluative Sciences (ICES). While legal data sharing agreements between ICES and data providers (e.g., healthcare organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified 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.

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