

Generational Patterns of Asthma Incidence among Immigrants to Canada over Two Decades

A Population-based Cohort Study

Dhenuka Radhakrishnan^{1,2}, Astrid Guttman^{3,4}, Teresa To^{3,4,5}, John Joseph Reisman^{1,2}, Braden D. Knight^{1,4,6,7}, Nassim Mojaverian⁴, Douglas G. Manuel^{4,6,8,9}, Jennifer L. Gommerman¹⁰, Kenneth Croitoru^{11,12}, and Eric I. Benchimol^{1,2,4,7}

¹Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada; ²Department of Pediatrics, ³Department of Family Medicine, and ⁴School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada; ⁵Hospital for Sick Children, Toronto, Ontario, Canada; ⁶Institute for Clinical Evaluative Science, Toronto, Ontario, Canada; ⁷Dalla Lana School of Public Health, ⁸Department of Immunology, and ⁹Department of Medicine, University of Toronto, Toronto, Ontario, Canada; ¹⁰Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; ¹¹Ontario Child Health Support Unit, Ottawa, Ontario, Canada; and ¹²Mount Sinai Hospital, SinaiHealthSystem, Toronto, Ontario, Canada

Abstract

Rationale: Canada, an industrialized country with high endemic asthma rates, is characterized by a large immigrant population.

Objectives: We sought to provide insight into the relative contribution of environmental exposure to asthma risk by comparing asthma rates among recent immigrants relative to long-term residents of Canada.

Methods: This was a population-based, retrospective cohort study performed using provincial health administrative data for all residents of Ontario, Canada. Residents with and without a diagnosis of asthma from fiscal years 1996–2012 were included. Individuals were categorized as being immigrants (landed in Canada after 1985) or long-term residents of Ontario by linkage with the Immigration, Refugees, and Citizenship Canada's Permanent Resident Database. We calculated the age- and sex-standardized incidence of asthma among residents of Ontario, and compared the incidence of asthma among immigrants and long-term residents using incidence rate ratios (IRRs).

Results: Analysis of approximately 11.7 million records showed that 2.2 immigrants arrived in Canada during the study period, with over 50% from East and South Asia and the Pacific. We found that asthma incidence was lower among immigrants compared with long-term residents (IRR = 0.30; 95% confidence interval = 0.30–0.30; $P < 0.001$). However, Ontario-born children of immigrants from most world regions had significantly higher asthma incidence compared with children of long-term residents (IRR = 1.44; 95% confidence interval = 1.43–1.45; $P < 0.001$). The overall incidence of asthma in Ontario decreased between 1996 and 2012 ($P_{\text{trend}} < 0.001$). Immigrants contributed to only a small proportion of the asthma incidence in Ontario, and changes within this group did not significantly affect trends in the overall Ontario population asthma incidence.

Conclusions: The higher asthma incidence seen among children of immigrants, but not in their parents, suggests that being born in Canada was critical for determining asthma risk. These findings support the importance of *in utero* and/or early life exposures on asthma development.

Keywords: asthma; immigrant; incidence; risk factors

(Received in original form March 18, 2018; accepted in final form November 2, 2018)

Supported by a New Investigator Award from the Canadian Institutes of Health Research, Canadian Association of Gastroenterology, and Crohn's and Colitis Canada (E.I.B.), by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program (E.I.B.), and a Canadian Institutes of Health Research Applied Chair in Reproductive and Child Health Services and Policy Research (A.G.).

The data set from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). Although data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/das. The full data set creation plan is available from the authors upon request. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of CIHI. The opinions, results, and conclusions reported in this paper are those of the authors, and are independent from the funding sources. No endorsement by ICES or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Author Contributions: Study conception and design: D.R., A.G., T.T., D.G.M., J.L.G., K.C., and E.I.B. Data analysis: B.D.K. and N.M. Results interpretation: all authors. Drafting and revision of manuscript: D.R., A.G., T.T., J.J.R., B.D.K., N.M., and E.I.B. Revision of manuscript and final approval: all authors.

Correspondence and requests for reprints should be addressed to Dhenuka Radhakrishnan, M.D., M.Sc., Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, K1H 8L1 Canada. E-mail: dradhakrishnan@cheo.on.ca.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 16, No 2, pp 248–257, Feb 2019

Copyright © 2019 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201803-187OC

Internet address: www.atsjournals.org

Although asthma has been historically common in Canada, with a reported prevalence ranging between 13% and 21% (1–3), there has been a steady reduction in new asthma cases over the last 20 years (4). This reduction in asthma incidence has overlapped with a period of increased immigration from Asian countries, where endemic asthma rates are much lower (5). In the last decade, 50% of immigrants arriving to Ontario, Canada's most populous province, were from South Asia (primarily from India, Pakistan, or Sri Lanka) and East Asia (primarily from China and Hong Kong) (6). The influence of immigration of individuals from world regions with low endemic asthma rates on overall asthma rates in Ontario has not been fully studied.

Previous measurements of asthma rates among immigrants from different parts of Asia have shown an increased risk of asthma proportional with the duration of living in Canada (2, 5). These studies also demonstrated higher rates of asthma among Canadian-born children of immigrants, relative to their parents (5, 7). Whether these findings translate to individuals immigrating from non-Asiatic regions of the world is not known.

In this study, we used population-based health administrative data to determine the incidence of asthma in immigrants to Canada and their children. Incidence of asthma was compared between immigrants from different regions of the world and long-term Ontario residents and their children, with the aim of providing further insight into the influence of environmental exposures on the development of asthma. We additionally explored the contribution of immigration to trends in overall asthma incidence in Ontario.

Methods

Setting and Study Design

This was a retrospective cohort study in which the health administrative data of all Ontario, Canada residents was linked to immigration data for the same population to compare the rates of new diagnoses of asthma ("incident asthma") among immigrants and nonimmigrant/long-term residents of Canada and their children. New asthma diagnoses were identified in this cohort between April 1, 1996 (fiscal year [FY] 1996) to March 31, 2013 (FY 2012).

Data Sources

Ontario health administrative data were accessed through the Institute for Clinical Evaluative Sciences (ICES). ICES is a nonprofit organization that operates under strict privacy and confidentiality legislation and allows researchers to conduct studies at a population-based level, given that more than 99% of Ontario residents are eligible for universal health coverage through the Ontario Health Insurance Plan (OHIP). The methods for linkage of the OHIP number of each subject with multiple additional datasets held at ICES to identify study variables and outcomes has been described in detail in a previous article (7). In brief, individuals with asthma were identified using the Ontario Asthma Surveillance Information System. This derived database includes all individuals in Ontario with asthma, as per the following validated algorithm: one hospitalization for asthma (as ascertained from the Canadian Institute for Health Information Discharge Abstract Database), or two outpatient physician visits for asthma (from the OHIP database) within a 2-year period. This algorithm has a sensitivity of 89% and a specificity of 72% among children, and a sensitivity of 84% and a specificity of 76% in adults, compared against a clinical diagnosis of asthma (8–10). The Immigration, Refugees, and Citizenship Canada Permanent Resident Database (IRCC-PR) includes all individuals who immigrated to Canada after 1985. Deterministic and probabilistic (using a combination of last and given name variants, date of birth, and sex) linkage methods were used to link this database to other Ontario health administrative databases with a reported linkage rate of 86.4% (11). The MOMBABY dataset contains all hospital births in Ontario (>98% of births). It was used to identify the children of immigrant and nonimmigrant mothers through probabilistic linkage using a combination of birth institution, postal code, and admission/discharge dates for children born between FY 1996 and FY 2002, and using a unique matching number for children born after FY 2002. This linkage method has a reported sensitivity of 96.1% and a specificity of 99.2% (12). All datasets used and the variables derived from them are described further in Table E1 in the online supplement.

Participants

Individuals who arrived to Canada after 1985 as identified from the IRCC-PR were defined as "immigrants," and those residing

in Canada before 1985 (i.e., long-term residents) are herein referred to as "nonimmigrants." This distinction was made as per the availability of IRCC-PR data. All Ontario residents were observed from FY 1996 and onward for the new development of asthma. Children could be defined as having newly diagnosed, or "incident asthma" if they were born in Ontario or arrived in Ontario within the first year of life, as they would be effectively observed for their entire lifetime. All other individuals (immigrant and nonimmigrant) were only defined as having newly diagnosed, or incident asthma if they had lived in Ontario for more than 5 years to allow for a 5-year look-back period without asthma-related health care visits. This 5-year look-back period was used to distinguish incident from prevalent cases, and is based on studies of other asthma and chronic disease cohorts, showing this duration without an asthma health care claim to be a sensitive window to identify "remission" of asthma (4, 13). Individuals (immigrants and long-term residents) who developed asthma less than 5 years after moving to Ontario would be classified as having "prevalent" asthma. Those with prevalent asthma were not included in the "at-risk" population or denominators for determining asthma incidence rates. Of note, Ontario health administrative data are available from 1991, and allows for observation of this 5-year look-back window for all individuals in this study.

The following exclusions were applied: Ontario residents without a valid OHIP number were excluded from the study. Individuals were analyzed within the study cohorts only up until they turned age 65 years to avoid bias due to misclassification of elderly patients with chronic obstructive pulmonary disease, as this is more prevalent in this age group than incident asthma. Individuals living in a rural neighborhood (community size <10,000 persons) were also excluded, as there would be underrepresentation of immigrants in these nonurban areas. Individuals whose date of last contact in health administrative data was more than 5 years in the past were excluded to account for those who may have moved out of province. Individuals with any missing variables were also excluded.

Main Outcomes

The age- and sex-standardized incidence of asthma over the period of 1996 to 2012 was

calculated among immigrants and nonimmigrants using the population of Ontario as the denominator. Age and sex standardization was performed using 2011 Statistics Canada information for Ontario as the reference. Differences in age- and sex-standardized asthma incidence rates over the entire time period from 1996 to 2012 were compared between immigrants and nonimmigrants from different regions of the world and within different age groups by calculating incidence rate ratios (IRR). IRR with 95% confidence intervals (CIs) were calculated using Poisson regression. We evaluated Poisson models for overdispersion by examining chi-square/degrees of freedom and ensured that variability was within expected for a Poisson distribution. Age groups were chosen to represent preschoolers (<5 yr), school-aged children (5–17.99 yr), and adults (18–64.99 yr). The world regions used were based on World Bank definitions (14) and are listed along with their represented countries in Table E2. Rates of asthma prevalence cases each year between 1996 and 2012 were also compared among immigrants and nonimmigrants from different world regions using prevalence ratios.

IRR for asthma with 95% CIs were compared among children born to immigrant mothers versus nonimmigrant mothers. IRR values were used to compare asthma rates among children within the different age groups defined previously here, and among children of immigrant mothers from different world regions.

Trends in asthma incidence over time within groups were determined using a linear test for trend (using a linear regression model). All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc.), and *P* values less than 0.05 were considered statistically significant. Ethical approval for this study was obtained from the Children's Hospital of Eastern Ontario and the Ottawa Hospital research ethics boards.

Results

A total of 11,740,942 individuals was included in this study, of whom 1,104,311 developed asthma for an overall Ontario period prevalence of 9.4%. There were 2,237,553 immigrants who arrived in Canada during the study period at a mean age of 29.4 (± 16.8 standard deviation [SD]) years.

The flow diagram for study cohort creation is shown in Figure 1, and further descriptive characteristics of the study population and immigrants are in Table 1 and Figure 2.

The standardized asthma incidence rates (per 1,000 person years) between 1996 and 2012 were lower among immigrants to Ontario compared with long-term residents of Ontario (Table 2).

When stratified by region of origin (Figure 3), the incidence of asthma between

1996 and 2012 was lower among immigrant children 0–5 years of age from all world regions compared with nonimmigrant residents of Ontario (IRR = 0.20; 95% CI = 0.19–0.21; *P* < 0.001). This was similarly the case for children 5–18 years of age (IRR = 0.24; 95% CI = 0.23–0.25; *P* < 0.001) and for adults 18–64.99 years of age (IRR = 0.59; 95% CI = 0.58–0.60; *P* < 0.001).

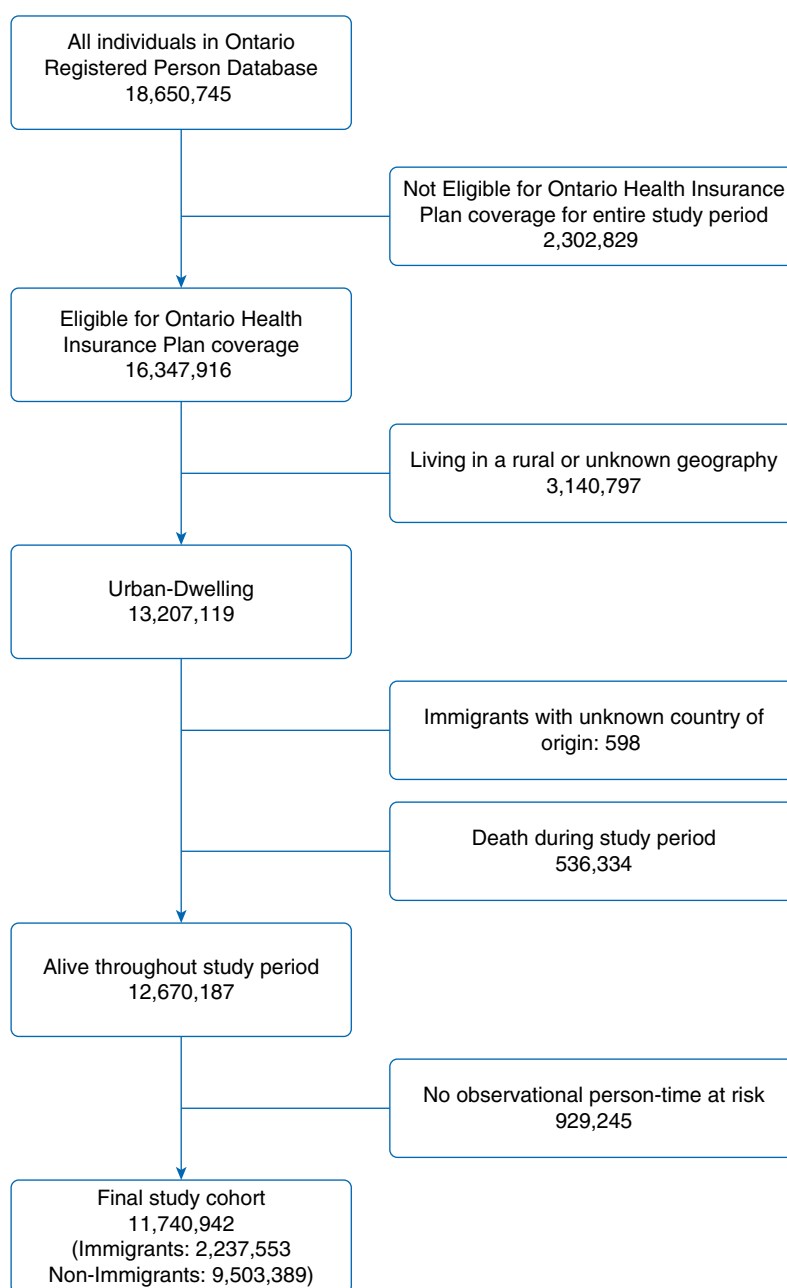


Figure 1. Flow diagram for study cohort creation.

Table 1. Description of the study population

Characteristic	Immigrants (<i>n</i> = 2,237,553)	Nonimmigrants (<i>n</i> = 9,503,389)	Children of Immigrants* (<i>n</i> = 422,305)	Children of Nonimmigrants* (<i>n</i> = 968,256)
Person years	23,726,716	119,305,039	2,677,271	7,263,805
Incident asthma cases, <i>n</i>	62,660	938,986	88,818	191,451
Asthma incidence per 1,000 person years (95% CI) [†]	2.64 (2.62–2.66)	7.87 (7.85–7.89)	33.17 (32.96–33.39)	26.36 (26.24–26.48)
Prevalent asthma cases, <i>n</i> (% [95% CI])	109,113 (4.9 [4.85–4.91])	995,198 (10.5 [10.45–10.49])	88,818 (21.03 [20.89–21.17])	191,451 (19.77 [19.68–19.86])
Age at asthma incidence, median (IQR)	40 (28–52)	10 (2–43)	1 (0–4)	1 (0–4)
Age <18 yr old at asthma incidence, <i>n</i> (%) [†]	7,437 (13.5)	530,700 (62.8)	88,818 (100.0)	191,451 (100.0)
Sex (% female)	1,151,308 (51.5)	4,798,094 (50.5)	205,078 (48.6)	471,500 (48.7)
Mean neighborhood income quintile distribution at start date of study eligibility (adult) or date of birth (child), <i>n</i> (%)				
Q1	858,120 (38.4)	1,889,468 (19.9)	150,328 (35.6)	164,458 (17.0)
Q2	517,768 (23.1)	1,874,066 (19.7)	98,176 (23.3)	179,791 (18.6)
Q3	370,542 (16.6)	1,898,139 (20.0)	77,407 (18.3)	204,533 (21.1)
Q4	279,416 (12.5)	1,919,803 (20.2)	60,581 (14.4)	226,827 (23.4)
Q5	201,250 (9.0)	1,888,729 (19.9)	35,315 (8.4)	191,846 (19.8)
Mean neighborhood income quintile distribution at asthma incident date, <i>n</i> (%)				
Q1	20,477 (32.7)	195,577 (20.8)	29,655 (33.4)	30,918 (16.2)
Q2	14,610 (23.3)	187,689 (20.0)	20,770 (23.4)	34,517 (18.0)
Q3	12,159 (19.4)	189,249 (20.2)	17,483 (19.7)	40,756 (21.3)
Q4	9,528 (15.2)	191,005 (20.3)	13,463 (15.2)	45,894 (24.0)
Q5	5,802 (9.3)	173,056 (18.4)	7,383 (8.3)	39,244 (20.5)

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; Q1–Q5 = income quintile 1 (lowest) to quintile 5.

*Limited to children born after 1996.

[†]Raw (unadjusted) incidence values are reported here.

The prevalence of asthma among immigrants was lower compared with nonimmigrants for all age groups and for all world regions, with the exception of very young children from Latin America and the Caribbean (prevalence rate ratio = 1.09; 95% CI = 1.03–1.16; *P* = 0.006) and from Eastern Europe and Central Asia (prevalence rate ratio = 1.13; 95% CI = 1.05–1.21; *P* = 0.005) who demonstrated a higher prevalence of asthma (Figure 4).

Children of Immigrant Mothers

We observed a higher standardized incidence of asthma among children of immigrants compared with the children of nonimmigrants (Table 3).

When stratified by world region (Figure 3), for children 0–17.99 years old, there was an increased incidence of asthma among children born to mothers from nearly all world regions (relative to children born to mothers who were long-term Ontario residents), with

the exception of Western Europe, North America, Eastern Europe, and Central Asia.

The incidence of asthma between 1996 and 2012 for nonimmigrant children (0–17.99 yr) decreased from 24.5 per 1,000 person years to 14.2 per 1,000 person years (mean difference = 10.31; 95% CI = 10.03–10.59; *P*_{trend} < 0.001; Figure 5). Similarly, the incidence of asthma decreased over time for nonimmigrant adults (18–64.99 yr), from 5.8 per 1,000 person years to 1.9 per 1,000 person years (mean

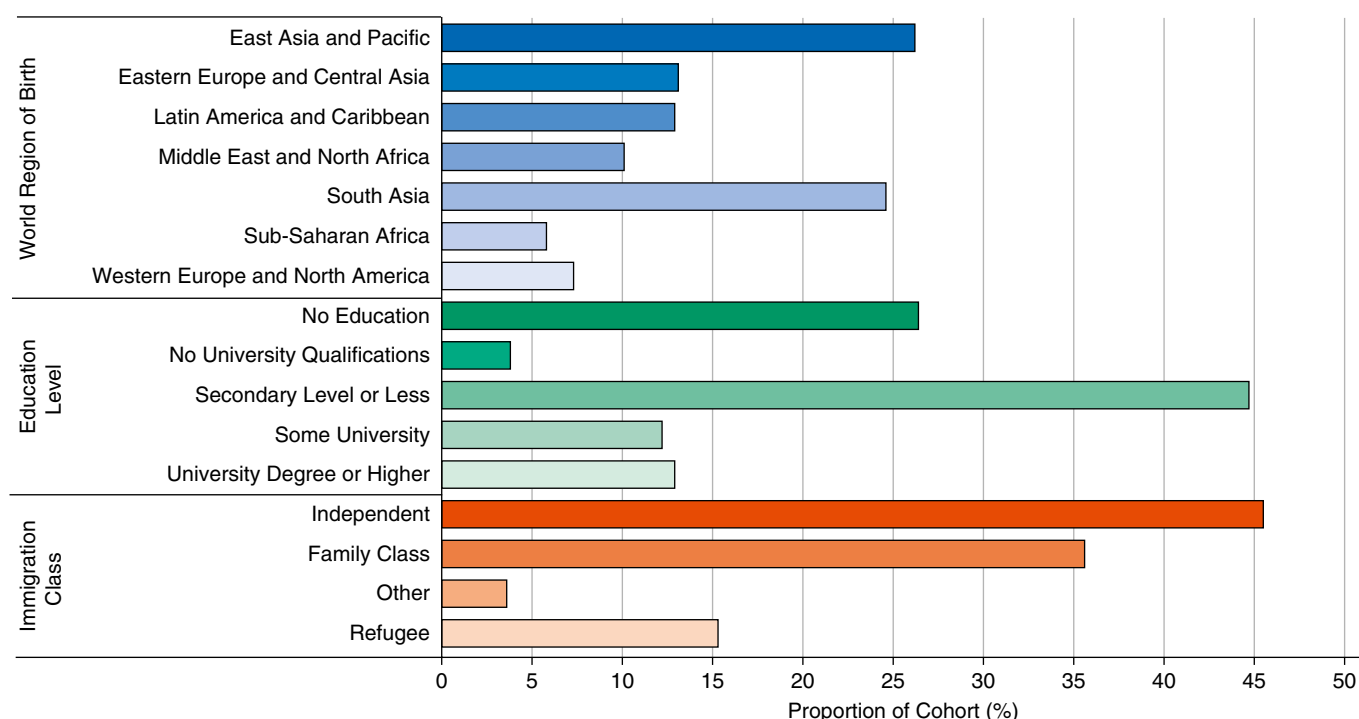


Figure 2. Baseline characteristics of immigrants.

difference = 3.88; 95% CI = 3.80–3.95; $P_{\text{trend}} < 0.001$). Although the incidence of asthma marginally decreased among immigrant children, from 0.27 per 1,000 person years to 0.21 per 1,000 person years (mean difference = 0.06; 95% CI = 0.03–0.09; $P_{\text{trend}} = 0.02$), it increased among immigrant adults from 0.29 per 1,000 person years to 0.59 per 1,000 person years (mean difference = –0.30; 95% CI = –0.32 to –0.28; $P_{\text{trend}} < 0.001$). The proportion of asthma incidence attributable to immigrants was less than 5% for any given study year, and thereby contributed

minimally to overall trends in the incidence of asthma in Ontario.

Discussion

In this study, we found that immigrants of all age groups from all world regions had a lower relative incidence of asthma compared with long-term residents of Canada; however, children of immigrants had an overall higher asthma incidence relative to children of nonimmigrants.

Our finding of a lower asthma incidence even among very young immigrant children compared with a similar age group

of nonimmigrant children suggests that it is not merely early exposure to the Canadian environment that increases asthma risk, as previously hypothesized (5). A previous study among Chinese residents of Vancouver, British Columbia, Canada showed that asthma rates were higher among Canadian-born Chinese adolescents, compared with those who immigrated from China, leading the authors to conclude that “duration of exposure” to Canadian environmental factors influences the prevalence of asthma (5). Similar conclusions have been drawn from studies

Table 2. Age- and sex-standardized incidence of asthma in Ontario (1996–2012) per 1,000 person years in immigrants and nonimmigrants and incidence rate ratios

Age Group	Immigrants			Nonimmigrants			IRR (Reference Group: Nonimmigrants)	95% CI
	At-Risk Person Years	Incidence*	95% CI	At-Risk Person Years	Incidence*	95% CI		
0 to <5 yr	152,114	9.32	8.84–9.82	7,668,262	46.42	46.27–46.58	0.20 [†]	0.19–0.21
5 to <18 yr	2,627,672	2.29	2.24–2.35	18,539,567	9.55	9.50–9.59	0.24 [†]	0.23–0.25
18–65 yr	19,051,447	2.49	2.47–2.52	74,785,563	4.23	4.22–4.25	0.59 [†]	0.58–0.60
Overall (all age groups)	21,831,233	2.52	2.49–2.54	100,993,392	8.37	8.35–8.39	0.30 [†]	0.30–0.30

Definition of abbreviations: CI = confidence interval; IRR = incidence rate ratio.

*Incidence is calculated per 1,000 person years.

[†] $P < 0.001$.

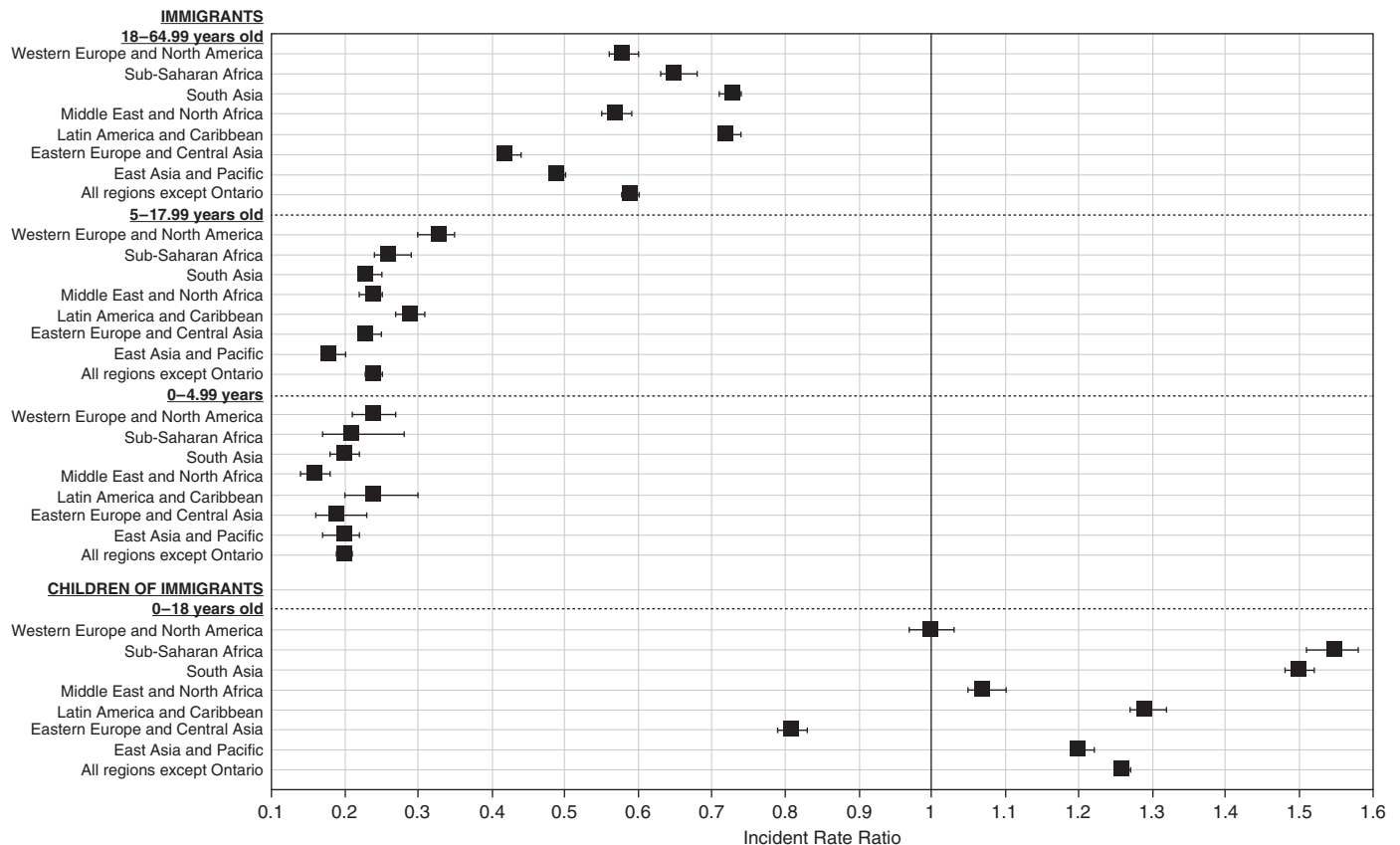


Figure 3. Incident rate ratios for the incidence of asthma among immigrants to Ontario (compared with nonimmigrants) and their children (compared with the children of nonimmigrants), stratified by age group and world region. Boxes, incident rate ratios; whiskers, upper and lower 95% confidence intervals.

done of different immigrant groups in the United Kingdom, with higher asthma prevalence noted among “black African” or South Asian immigrants who had been born in the United Kingdom, rather than those who had immigrated within the last 5 years (15, 16). Our findings were comparable, with a higher incidence of asthma seen in the children of immigrants from China and Hong Kong (as well as other world regions) than in the immigrants themselves. However, in this longitudinal study, we also found that the association between increased asthma risk with exposure to the Canadian environment pertains to Canadian-born children of immigrants, and not to immigrants born in other countries, even if arriving to Canada at a very young age. This finding conforms with previous literature showing that, beyond the duration of exposure, it is likely the timing of exposure to various factors in the Canadian environment that is most critical for triggering asthma susceptibility (17). These environmental factors with potential

positive or negative influence on asthma susceptibility include not only outdoor air pollution (18), but also bacterial exposure (19), inhaled allergens (20), specific types of respiratory viruses, dietary factors (21), as well as social and cultural or lifestyle factors (22) (e.g., breast feeding [23–25], smoking [14, 26], antibiotic use [27, 28]). Although all of these classes of exposure may exist in all world regions, the particular type or dose of these factors may vary for those in Canada compared with other places. Furthermore, there is mounting evidence that early exposures to the *in utero* milieu during gestation (e.g., including nutritional elements [25, 29] or stress-related hormones [30–32]), or the maternal vaginal or gut microbiome at delivery (which would be largely determined by environmental factors) can influence the development of the airways and immune system and downstream susceptibility to developing asthma (33–35). This evidence supports the importance of place of birth on lifetime asthma risk, as seen in the current

study. The association between timing of exposure to this broad definition of the Canadian environment and higher risk for asthma appears to be more pronounced among children born to mothers from certain world regions, such as Sub-Saharan Africa or South Asia, where endemic asthma rates have traditionally been low. This observation suggests that there may be some “unmasking” of a higher susceptibility to asthma among children of mothers from these regions when exposed to the Canadian environment at birth, perhaps due to gene–environment interactions, or epigenetic phenomenon (36–38).

Another finding in this study is that a higher proportion (>50%) of immigrants and children of immigrants fell into the lower-income quintiles relative to nonimmigrants. Previous Canadian research has shown a relationship between lower socioeconomic status and increased incidence and prevalence of asthma (39, 40). As such, we would have expected this to translate to a higher asthma incidence

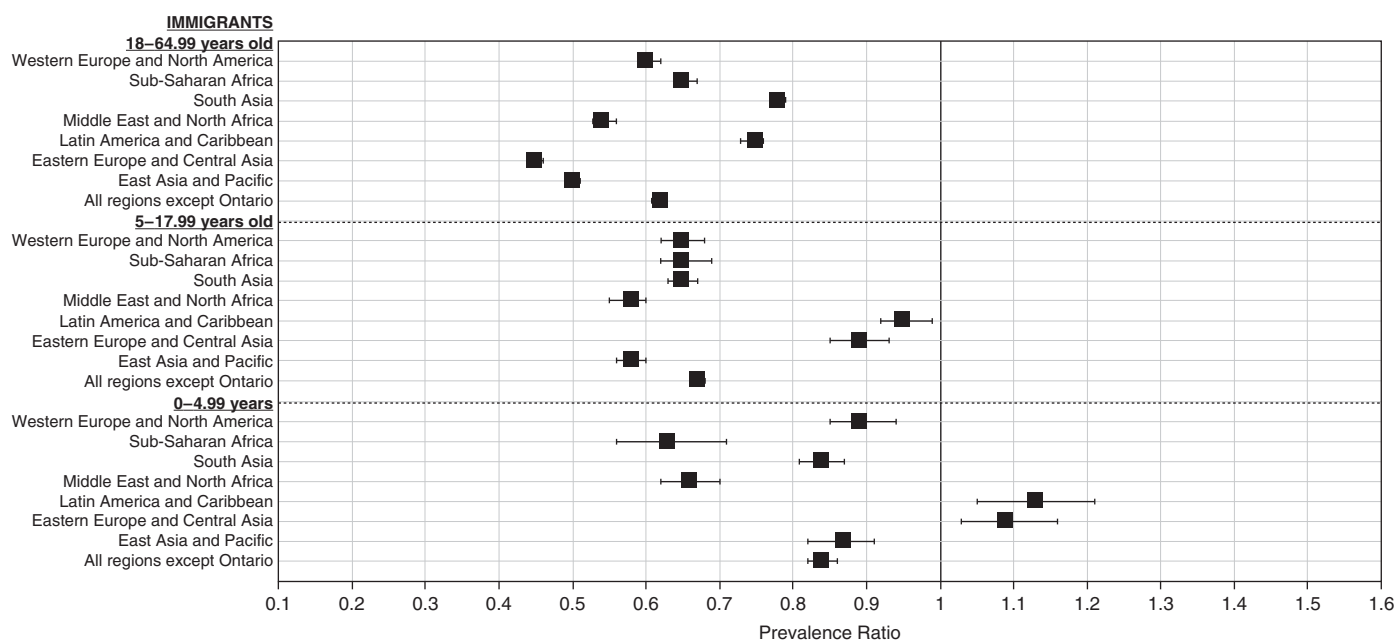


Figure 4. Prevalence ratios comparing the prevalence of asthma among immigrants to Ontario to nonimmigrants (reference), stratified by age group and world region between 1996 and 2012.

among immigrants. One possible explanation for our discordant finding of a lower asthma incidence among immigrants, despite their lower socioeconomic status, is due to the “healthy immigrant effect,” or the observation that individuals who immigrate to Canada are healthier than Canadian-born residents. This is thought to relate to the immigration selection process or self-selection by immigrants who are more healthy and willing to relocate to a new country (41, 42). This healthy immigrant effect may also explain the finding of lower asthma incidence and prevalence among individuals from other high-income western countries, such as the United States and

within Europe, compared with Canada, as seen in this and a few prior studies (4, 43). However, the protective advantage of the healthy immigrant effect has also been shown to decrease with years spent in Canada, and may then explain why an increased asthma incidence was observed among subsequent generations (i.e., children) of immigrants.

In addition to lower asthma incidence, we did also note an overall lower prevalence of asthma among immigrants of all ages, though there was some variability in this based on the world region of origin. Variable asthma rates among immigrants from different world regions could be due to

differences in genetic susceptibility to asthma (44), environmental factors, as mentioned previously here, or perhaps the interaction between genetic and environmental factors (38). Further studies at the patient level are necessary to better understand these potential associations.

In this study, we also noted a decreased incidence of asthma in Ontario over time, particularly among both nonimmigrants and immigrant children. The decrease in asthma incidence in this study is concordant with the results of other studies of asthma rates in Canada and other industrialized countries (4). Our finding of a decrease in overall Ontario asthma incidence was

Table 3. Age- and sex-standardized incidence of asthma in Ontario (1996–2012) per 1,000 persons in the Ontario-born children of immigrants and nonimmigrants and incidence rate ratios

Age Group	Children of Immigrants			Children of Nonimmigrants			IRR (Reference Group: Nonimmigrants)	95% CI
	At-Risk Person Years	Incidence*	95% CI	At-Risk Person Years	Incidence	95% CI		
0 to <5 yr	1,727,132	50.17	49.83–50.50	5,136,110	41.93	41.75–42.11	1.20 [†]	1.19–1.21
5 to <18 yr	1,795,851	11.31	11.15–11.47	7,972,892	9.11	9.04–9.18	1.24 [†]	1.22–1.26
18–65 yr	94,584	1.89	1.63–2.19	960,499	2.36	2.27–2.46	0.79 [†]	0.68–0.92
Overall (all age groups)	3,617,594	29.61	29.44–29.79	14,069,657	20.63	20.56–20.71	1.44 [†]	1.43–1.45

Definition of abbreviations: CI = confidence interval; IRR = incidence rate ratio.

*Incidence is calculated per 1,000 person years.

[†] $P < 0.001$.

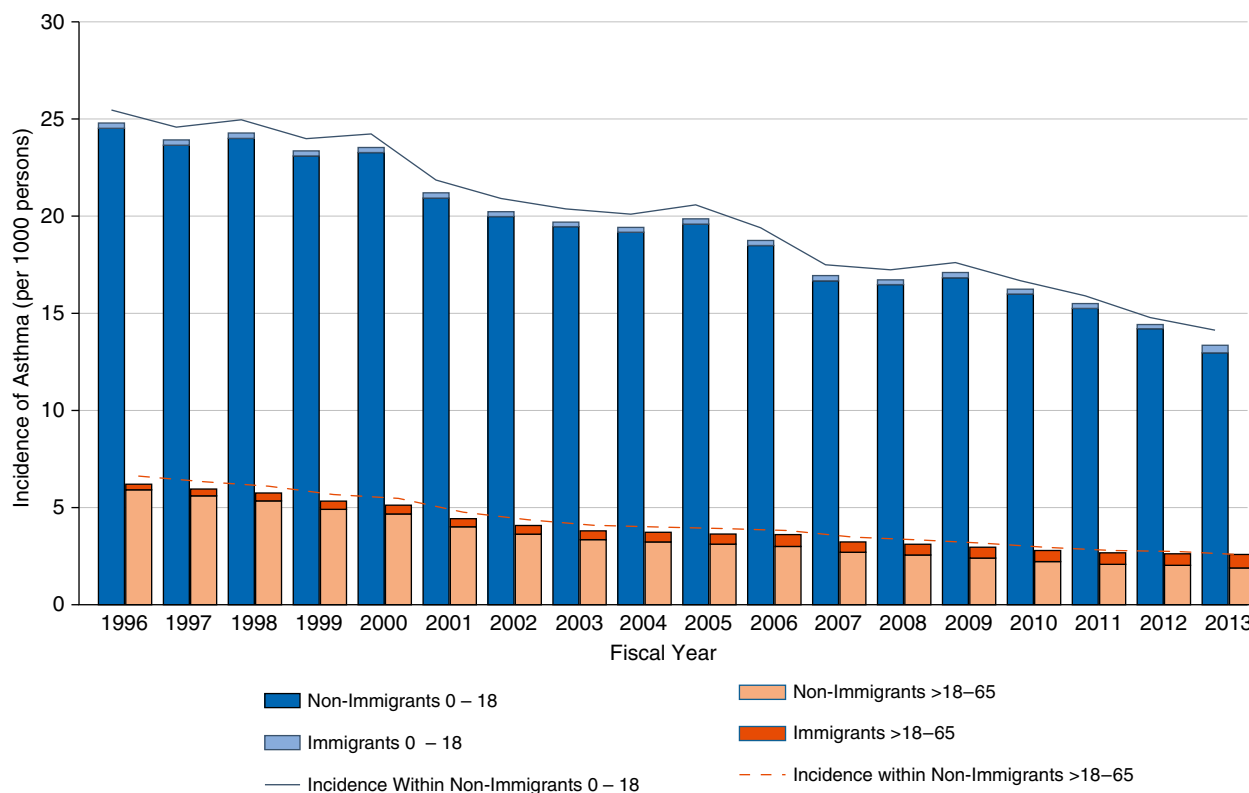


Figure 5. Annual age- and sex-standardized incidence of asthma in Ontario, Canada residents from 1996 to 2012, stratified by age group and immigrant status. The denominators for the bar graphs above include the entire population of Ontario for each age group, whereas denominators for the line graphs include the nonimmigrant population only.

despite an observed small increase in asthma incidence among adult immigrants over time. Therefore, regardless of rising immigration to Ontario from world regions where endemic asthma rates are low (45), a dilutional effect does not explain the reduction in asthma incidence observed in Ontario over time. Other factors, such as reduced rates of tobacco smoking (46) and increased breast feeding (47, 48), may better explain the fall in asthma incidence, though these mechanisms have not been proven.

The use of population-based health administrative data in this study provided significant power and the ability to generalize results across the population over two decades. However, research with administrative data does have some limitations. For example, we used world regions to explore the risk of asthma within different immigrant populations. However, this classification is based on World Bank economic classifications, and may have restricted ability to discern different ethnic groups, genotypes, and environmental exposures, all of which can influence the

development of asthma. Furthermore, though we used validated algorithms to link individuals with the Canadian immigration dataset, this linkage may have been more robust in some immigrant groups compared with others (11). Similarly, although validated algorithms were used to identify the definition of asthma, there is risk of misclassification bias, especially because certain immigrant groups may have either higher or lower use of routine and urgent health services compared with nonimmigrants, thereby influencing their likelihood of being identified as having asthma from within health administrative data. The use of a 5-year look-back period may not be long enough to distinguish incident asthma among immigrants, especially because asthma may be underdiagnosed (49, 50) in many developing countries, and there could be a delay in asthma diagnosis even after arrival to Canada. Another reason for potential delay in asthma diagnosis is the fact that immigrants are not immediately eligible for provincial (OHIP) health care coverage. For most individuals, there is a

3-month waiting period before they are eligible, but for immigrants who claim refugee status, this waiting period is variable, and can be longer than 3 months. Immigrants who were diagnosed with asthma after arrival in Canada, but had less than 5 years look-back data available, or were not yet covered under OHIP, would not have been included in our study cohort of individuals with incident asthma. These various potential misclassifications may have falsely lowered the observed asthma incidence in immigrants. As we did not observe asthma prevalence to be higher among immigrants, this leads us to believe that the possible misclassification of incident and prevalent asthma among immigrants may be insignificant, and likely did not affect the overall direction of our observed findings. Furthermore, this potential for misclassification would not have influenced the finding of higher asthma incidence among Ontario-born children of immigrants in this study. Finally, although we use the terms “immigrant” and “nonimmigrant” in this study, it is to be noted

that some individuals who may have immigrated to Canada before 1985 would be misclassified as nonimmigrants. However, as this is a study primarily of incident asthma, and because new asthma diagnosis is less common in older adults, we believe that this additional potential misclassification would not significantly affect the overall study results.

Over the past few decades, asthma incidence has decreased in Ontario, Canada, and relative asthma rates have remained lower among immigrants. However,

Ontario-born children of immigrants have a significantly increased asthma risk compared with the children of nonimmigrants. Our study suggests that very early life or *in utero* exposures to environmental factors in Canada are important in activating this higher asthma risk among the children of immigrants. The impact of the higher incidence of asthma in Canadian-born children of immigrants on health services utilization and asthma severity remains to be explored. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors acknowledge GEMINI (www.geministudy.ca) for their support of the initial conception of this work and related studies. GEMINI was funded by the Connaught Foundation and the Canadian Institutes of Health Research. This study was conducted at the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care.

References

- Statistics Canada. Changes in the prevalence of asthma among Canadian children, Health Reports, Vol. 19 No. 2, catalogue number 82-003-XWE. 2008 Jan 1 [updated 2015 Jul 17; accessed 2017 May 18]. Available from <https://www150.statcan.gc.ca/n1/pub/82-003-x/82008002/article/10551/5202470-eng.htm>.
- Moerman JN, Ratjen F, Subbarao P, Sears MR, Anand SS, Stanojevic S. The prevalence of asthma in Canadian children of South Asian descent. *Pediatr Pulmonol* 2014;49:43–48.
- Ontario Asthma Surveillance Information System (OASIS). Data tables, asthma incidence and prevalence. 2012 Jan 1 [updated 2017 Jan 1; accessed 2017 Feb 16]. Available from: <http://lab.research.sickkids.ca/oasis/data-tables/>.
- Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996–2005: a population study. *Am J Epidemiol* 2010;172:728–736.
- Wang HY, Wong GW, Chen YZ, Ferguson AC, Greene JM, Ma Y, et al. Prevalence of asthma among Chinese adolescents living in Canada and in China. *CMAJ* 2008;179:1133–1142.
- Benchimol EI, Mack DR, Guttman A, Nguyen GC, To T, Mojaverian N, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. *Am J Gastroenterol* 2015;110:553–563.
- Benchimol EI, Manuel DG, To T, Mack DR, Nguyen GC, Gommerman JL, et al. Asthma, type 1 and type 2 diabetes mellitus, and inflammatory bowel disease amongst South Asian immigrants to Canada and their children: a population-based cohort study. *PLoS One* 2015;10:e0123599.
- To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, et al. Case verification of children with asthma in Ontario. *Pediatr Allergy Immunol* 2006;17:69–76.
- Yang CL, To T, Foty RG, Stieb DM, Dell SD. Verifying a questionnaire diagnosis of asthma in children using health claims data. *BMC Pulm Med* 2011;11:52.
- To T, Dell S, Dick P, Cicutto L, MacLusky I, Tassoudji M, et al. Defining asthma in children for surveillance [abstract]. Presented at the 79th Conference of the American Thoracic Society. Orlando, FL. *Am J Respir Crit Care Med* 2004;169:A383.
- Chiu M, Lebenbaum M, Lam K, Chong N, Azimae M, Iron K, et al. Describing the linkages of the immigration, refugees and citizenship Canada permanent resident data and vital statistics death registry to Ontario's administrative health database. *BMC Med Inform Decis Mak* 2016;16:135.
- Provincial perinatal report. Ottawa: Provincial Perinatal Surveillance System Committee; 2006.
- To T, Gershon A, Wang C, Dell S, Cicutto L. Persistence and remission in childhood asthma: a population-based asthma birth cohort study. *Arch Pediatr Adolesc Med* 2007;161:1197–1204.
- The World Bank. Country and lending groups. 2016 May 6 [accessed 2017 Feb 14]. Available from: <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.
- Netuveli G, Hurwitz B, Sheikh A. Ethnic variations in incidence of asthma episodes in England & Wales: national study of 502,482 patients in primary care. *Respir Res* 2005;6:120.
- Kuehni CE, Strippoli MP, Low N, Silverman M. Asthma in young south Asian women living in the UK: the importance of early life. *Clin Exp Allergy* 2007;37:47–53.
- Turner SW, Young S, Goldblatt J, Landau LI, Le Souëf PN. Childhood asthma and increased airway responsiveness: a relationship that begins in infancy. *Am J Respir Crit Care Med* 2009;179:98–104.
- Gasana J, Dillikar D, Mendy A, Forno E, Ramos Vieira E. Motor vehicle air pollution and asthma in children: a meta-analysis. *Environ Res* 2012;117:36–45.
- Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55:S2–S10.
- Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;181:E181–E190.
- Litonjua AA. Dietary factors and the development of asthma. *Immunol Allergy Clin North Am* 2008;28:603–629. [ix.]
- Panico L, Bartley M, Marmot M, Nazroo JY, Sacker A, Kelly YJ. Ethnic variation in childhood asthma and wheezing illnesses: findings from the Millennium Cohort Study. *Int J Epidemiol* 2007;36:1093–1102.
- Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139:261–266.
- Mihirshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D, et al.; CAPS Team. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy* 2007;37:671–679.
- Willers SM, Devereux G, Craig LC, McNeill G, Wijga AH, Abou El-Magd W, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax* 2007;62:773–779.
- Hofhuis W, de Jongste JC, Merkus PJ. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. *Arch Dis Child* 2003;88:1086–1090.
- McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med* 2002;166:827–832.
- Jedrychowski W, Gałaś A, Whyatt R, Perera F. The prenatal use of antibiotics and the development of allergic disease in one year old infants: a preliminary study. *Int J Occup Med Environ Health* 2006;19:70–76.
- Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fitó N, Antó JM, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clin Exp Allergy* 2007;37:518–525.
- Andersson NW, Hansen MV, Larsen AD, Hougaard KS, Kolstad HA, Schlünssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. *Allergy* 2016;71:15–26.
- Radhakrishnan D, Shariff SZ, To T. The influence of prenatal mental health service use on the incidence of childhood asthma: a population-based cohort study. *J Asthma* (In press)

- 32 von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J Allergy Clin Immunol* 2002; 109:923–928.
- 33 Stiemsma LT, Turvey SE. Asthma and the microbiome: defining the critical window in early life. *Allergy Asthma Clin Immunol* 2017;13:3.
- 34 Barfod KK, Roggenbuck M, Hansen LH, Schjørring S, Larsen ST, Sørensen SJ, *et al.* The murine lung microbiome in relation to the intestinal and vaginal bacterial communities. *BMC Microbiol* 2013;13: 303.
- 35 Jackson DJ, Gern JE, Lemanske RF Jr. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol* 2017;139:379–386.
- 36 DeVries A, Vercelli D. Epigenetic mechanisms in asthma. *Ann Am Thorac Soc* 2016;13:S48–S50.
- 37 Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. *Am J Respir Crit Care Med* 2008;177: 567–573.
- 38 Zhang G, Candelaria P, Mäkelä JM, Khoo SK, Hayden MC, von Hertzen L, *et al.* Disparity of innate immunity-related gene effects on asthma and allergy on Karelia. *Pediatr Allergy Immunol* 2011;22: 621–630.
- 39 Kozyrskyj AL, Kendall GE, Jacoby P, Sly PD, Zubrick SR. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100: 540–546.
- 40 Cope SF, Ungar WJ, Glazier RH. Socioeconomic factors and asthma control in children. *Pediatr Pulmonol* 2008;43:745–752.
- 41 Statistics Canada. Health Reports: the healthy immigrant effect and mortality rates. 2015 [accessed 2017 Feb 14]. Available from: <http://www.statcan.gc.ca/pub/82-003-x/2011004/article/11588-eng.htm>.
- 42 Vang Z, Sigouin J, Flenon A, Gagnon A. The healthy immigrant effect in Canada: a systematic review; Population change and lifecourse strategic knowledge cluster Discussion Paper Series/Un réseau stratégique de connaissances changements de population et parcours de vie Document de travail. 2015 [accessed 2017 Feb 14]. Available from: <http://ir.lib.uwo.ca/pclc/vol3/iss1/4>.
- 43 Lawson JA, Brozek G, Shpakou A, Fedortsiv O, Vlaski E, Beridze V, *et al.* An international comparison of asthma, wheeze, and breathing medication use among children. *Respir Med* 2017;133:22–28.
- 44 Schwartz DA. Gene–environment interactions and airway disease in children. *Pediatrics* 2009;123:S151–S159.
- 45 Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, *et al.*; ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007;62: 758–766.
- 46 Statistics Canada. Smoking. 2017 Mar 22 [accessed 2017 May 18]. Available from: <http://www.statcan.gc.ca/eng/help/bb/info/smoking>.
- 47 Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. *Am J Epidemiol* 2014;179:1153–1167.
- 48 Statistics Canada. Health at a glance. 2015 Nov 27 [accessed 2017 May 18]. Available from: <http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11879-eng.htm>.
- 49 World Health Organization–Media Centre. Asthma. 2017 Jan 1 [accessed 2017 May 18]. Available from: <http://www.who.int/mediacentre/factsheets/fs307/en/>.
- 50 Zar HJ, Levin ME. Challenges in treating pediatric asthma in developing countries. *Paediatr Drugs* 2012;14:353–359.

Online Data Supplement

Generational Patterns of Asthma Incidence among Immigrants to Canada over Two Decades: A Population-based Cohort Study

Dhenuka Radhakrishnan M.D., M.Sc., Astrid Guttman MDCM, M.Sc., Teresa To PhD., John Joseph Reisman M.D., MBA., Braden D. Knight M.Sc., Nassim Mojaverian M.Sc., Douglas G. Manuel M.D., M.Sc., Jennifer L. Gommerman Ph.D., Kenneth Croitoru MDCM, Eric I. Benchimol M.D., Ph.D.

Online Supplementary Tables

Supplementary Table I. Institute for Clinical Evaluative Sciences datasets used for cohort, variable and outcome definitions

Dataset	Dates available* (Dates accessed)	Description of dataset, variables and outcomes
OHIP	1991 – 2015 (1991 – 2013)	Record of all physician billed medical services (diagnoses and dates) - Used to define incident and prevalent asthma (i.e. used to populate OASIS database)
CIHI-DAD	1988 – 2015 (1991 – 2013)	Record of all hospital admissions (diagnoses and dates) - Used to define incident and prevalent asthma (i.e. used to populate OASIS database)
OASIS	1991 – 2015 (1991 -2013)	Derived cohort of all incident and prevalent cases of asthma since 1996 - Used to identify study cohort
MOMBABY	1988 – 2015 (1996 – 2013)	Linked health records of mothers and their child(ren) for in-hospital birth, derived from CIHI-DAD. - Used to identify linked pairs of mothers and their children
Canadian Census	Conducted every 4 years (1991, 1996, 2001, 2006)	Survey of all Canadian households; contains information on postal code, income and other household variables - Used to define neighbourhood income quintile, and provide information for age- sex- standardization calculations
RPDB	1991-2015 (1991 – 2013)	A population-based registry maintained by the Ontario government. It provides basic demographic information on individuals who have ever received an Ontario health card number. - Used to obtain information on date of birth, death, sex - Allows linkage across datasets by postal code for determination of neighbourhood income quintile and rurality

IRCC-PR	1985 – 2015 (1985 – 2013)	Contains information for all immigrants to Canada - Used to define date of arrival to Canada, immigration class (refugee, immigrant), highest education level; - Immigrants = those who arrived after 1985, and non-immigrants = those residing in Canada prior to 1985
---------	------------------------------	---

Earliest access dates listed represent the earliest limits of data availability

OHIP: Ontario Health Insurance Plan, CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database, OASIS: Ontario Asthma Surveillance Information System, MOMBABY: linked mother-baby dataset, RPDB: Ontario Registered Persons Database, IRCC-PR: Immigration, Refugees and Citizenship Canada Permanent Resident database

Supplementary Table II: World Regions and Country of Birth¹

East Asia and Pacific
Asia, NES
Brunei
Cambodia
China, People's Republic
Cooke Islands
Fiji
French Polynesia
Guam
Hong Kong
Indonesia
Japan
Kiribati
Korea, Democratic Republic
Lao PDR
Macau
Malaysia
Marinas
Marshall Islands
Micronesia, Fed. Sts
Mongolia
Myanmar
Nauru
New Caledonia
Northern Mariana Islands
Palau
Papa New Guinea
Philippines

Pitcairn Island
Samoa
Sikkim
Singapore
Solomon Islands
Taiwan
Thailand
Tibet
Timor-Leste
Tuvalu
Tonga
Vanuatu
Vietnam
Wallis and Futuna
South Asia
Afghanistan
Bangladesh
Bhutan
India
Maldives
Nepal
Pakistan
Sri Lanka
Middle East and North Africa
Algeria
Bahrain
Cyprus
Egypt, Arab Republic
Iran, Islamic Republic
Iraq
Israel
Jordan
Kuwait
Lebanon
Libya
Morocco
Oman
Palestinian Authority (West Bank and Gaza)
Qatar

Saudi Arabia
Syrian Arab Republic
Tunisia
United Arab Emirates
Western Europe and North America
Australia, NES
Australia
Austria
Andorra
Azores
Belgium
Canada
Canary Islands
Channel Islands
Denmark
Europe, NES
Finland
France
Germany
Gibraltar
Greece
Greenland
Holy See
Iceland
Italy
Ireland
Liechtenstein
Luxembourg
Madeira
Malta
Monaco
New Zealand
Norway
Portugal
San Marino
Spain
Sweden
Switzerland
The Netherlands

United Kingdom (Great Britain, Wales, Scotland)
United States
Sub-Saharan Africa
Africa, NES
Angola
Benin
Botswana
Burkina Faso
Burundi
Cameroon
Cape Verde
Central African Republic
Chad
Comoros
Congo Democratic Republic & People's Republic
Djibouti, Republic of
Eritrea
Ethiopia
Gabon
Gambia
Ghana
Guinea-Bissau
Ivory Coast, Republic of
Kenya
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Mauritius
Mayotte
Mozambique
Namibia
Niger
Nigeria
Reunion
Rwanda
Sao Tome and Principe

Senegal
Seychelles
Sierra Leone
Somalia
South Africa
St. Helena
Sudan
Swaziland
Tanzania
Togo
Uganda
Western Sahara
Zambia
Zimbabwe
Eastern Europe and Central Asia
Albania
Armenia
Azerbaijan
Belarus
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic
Estonia
Georgia
Hungary
Kazakhstan
Kosovo
Kyrgyz Republic
Latvia
Lithuania
Macedonia, FYR
Moldova
Poland
Romania
Russian Federation
Serbia and Montenegro
Slovakia
Slovenia

Union of Soviet Socialist Republics
Tajikistan
Turkey
Turkmenistan
Ukraine
Uzbekistan
Yugoslavia
Latin America and the Caribbean
Anguilla
Antigua and Barbuda
Argentina
Aruba
Bahamas
Barbados
Belize
Bermuda
Bolivia
Brazil
British Virgin Islands
Cayman Islands
Central America, NES
Chile
Columbia
Costa Rica
Cuba
Dominica
Dominican Republic
Ecuador
El Salvador
Falkland Islands
French Guiana
Grenada
Guadeloupe
Guatemala
Guyana
Haiti
Honduras
Jamaica
Martinique

Mexico
Montserrat
The Netherland Antilles
Nicaragua
Panama
Paraguay
Peru
Puerto Rico
South America, NES
St. Kitts and Nevis
St. Lucia
St. Maarten
St. Martin
St. Vincent and the Grenadines
Surinam
Trinidad and Tobago
Turks and Caicos
United States Virgin Islands
Uruguay
Venezuela, RB
West Indies, NES

NES = Not elsewhere specified, PDR = People's Democratic Republic,
Fed. Sts = Federal States, FYR = Former Yugoslav Republic, RB = Bolivarian Republic

References:

1. The World Bank: Country and Lending Groups. Available:.. (Accessed Feb14, 2017, at <http://data.worldbank.org/about/country-classifications/country-and-lending-groups>.)