

# Incidence of Inflammatory Bowel Disease in South Asian and Chinese People: A Population-Based Cohort Study from Ontario, Canada

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**Background:** Inflammatory bowel disease (IBD) is now a global disease with incidence increasing throughout Asia.

**Aim:** To determine the incidence of IBD among South Asians and Chinese people residing in Ontario, Canada's most populous province.

**Methods:** All incident cases of IBD in children (1994–2015) and adults (1999–2015) were identified from population-based health administrative data. We classified South Asian and Chinese ethnicity using immigration records and surnames. We determined standardized incidence of IBD and adjusted incidence rate ratio (aIRR) in South Asians and Chinese compared to the general population.

**Results:** Among 16,230,638 people living in Ontario, standardized incidence of IBD per 100,000 person-years was 24.7 (95% CI 24.4–25.0), compared with 14.6 (95% CI 13.7–15.5) in 982,472 South Asians and with 5.4 (95% CI 4.8–5.9) in 764,397 Chinese. The risk of IBD in South Asians was comparable to the general population after adjusting for immigrant status and confounders (aIRR 1.03, 95% CI 0.96–1.10). South Asians had a lower risk of Crohn's disease (CD) (aIRR 0.66, 95% CI 0.60–0.77), but a higher risk of ulcerative colitis (UC) (aIRR 1.47, 95% CI 1.34–1.61). Chinese people had much lower rates of IBD (aIRR 0.24, 95% CI 0.20–0.28), CD (aIRR 0.21, 95% CI 0.17–0.26), and UC (aIRR 0.28, 95% CI 0.23–0.25).

**Conclusion:** Canadians of South Asian ethnicity had a similarly high risk of developing IBD compared to other Canadians, and a higher risk of developing UC, a finding distinct from the Chinese population. Our findings indicate the importance of genetic and environmental risk factors in people of Asian origin who live in the Western world.

**Keywords:** inflammatory bowel disease, ulcerative colitis, Crohn's disease, incidence, ethnicity, epidemiology, South Asian, Chinese

## Introduction

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the bowel and comprised of two major sub-types, Crohn's disease (CD) and ulcerative colitis (UC).<sup>1</sup> Whereas incidence of IBD is stabilizing in the Western World, it is rapidly increasing in newly industrialized countries.<sup>2</sup> Canada has among the highest rates in the world, and prevalence is projected to rise from 0.7% in 2018 to 1% in 2030.<sup>3</sup> Ontario, Canada's most populous province, has a highly diverse population, with visible minorities representing 29% of residents.<sup>4,5</sup> Previous population-based studies from Ontario have demonstrated lower rates of IBD among immigrants from South and East Asia relative to non-immigrants, but rates among Canadian-born children of South

Asian immigrants were comparable to the children of non-immigrants.<sup>6</sup> However, this study evaluated only immigrants, and not the influence of ethnicity in people who were not immigrants. To understand the role of environmental risk factors in the pathophysiology of IBD, it is important to understand the role of ethnicity in IBD epidemiology. In this population-based study, we described differences in the incidence of IBD in people of South Asian and Chinese ethnicity compared to other residents of Ontario.

## Methods

### Study Design, Setting and Study Population

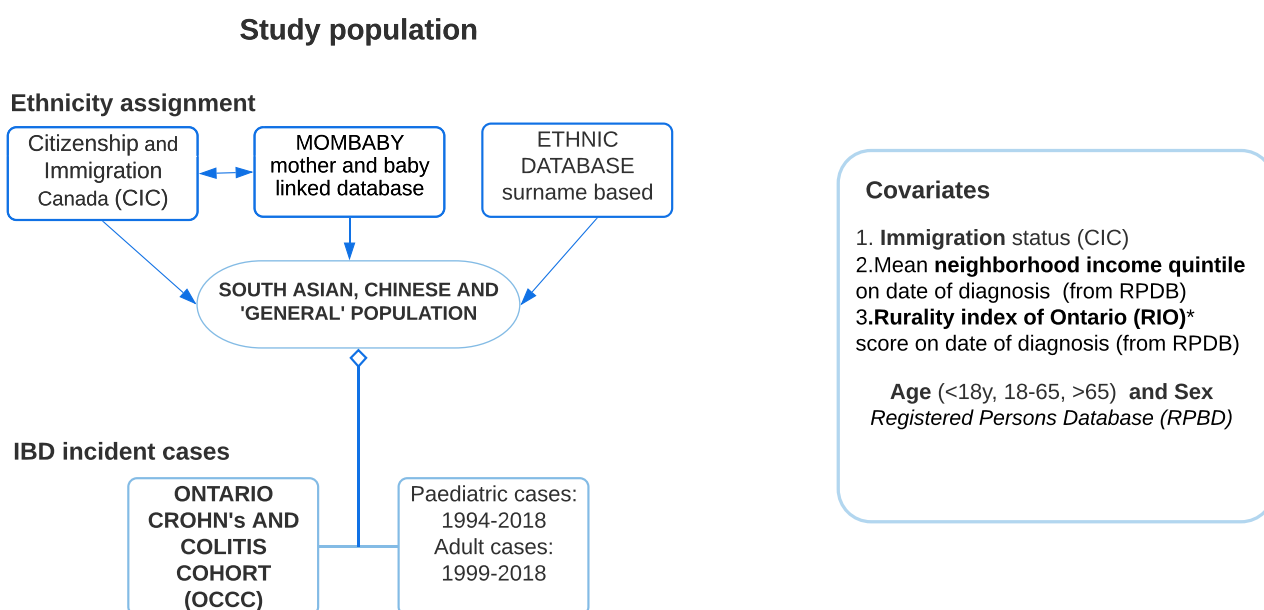
We conducted a cohort study using the population-based health administrative data for Ontario, Canada (population 14.4 million). We included all residents of Ontario registered for universal healthcare (>99% of the population) from fiscal year (FY) 1991 to 2018 (ie, April 1, 1991 to March 31, 2019). We excluded individuals with missing date of birth or missing valid ICES unique encrypted identification number (IKN), or those who left Ontario and then returned during the study period (due to incomplete administrative data). We excluded those with missing data for both exposure (ethnicity) and independent variables (confounders). Ontario residents were followed forward within the databases to determine whether they were diagnosed with IBD before

April 1, 2019. This study was approved by the research ethics boards of the London School of Hygiene and Tropical Medicine (21620/RR/18073) and the Children's Hospital of Eastern Ontario (19/08PE).

### Data Sources

Ontario health administrative data is held at ICES, an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The datasets were linked deterministically using unique encoded identifiers (IKN) and analyzed at ICES. We identified all individuals from the Registered Persons Database (RPDB), which contains information on all legal residents of Ontario registered for universal health care under the Ontario Health Insurance Plan (OHIP). RPDB also contains information including date of birth, location of residence (postal codes), sex and mean neighbourhood income quintile.

We linked three databases to characterize the South Asian and Chinese populations, and other Ontario residents defined as "general" (Figure 1). The ETHNIC database assigns ethnicity based on surnames.<sup>7</sup> South Asian surnames are largely of Hindu, Sikh, Bhutan and Sri Lankan origin, and surnames of Christian and Muslim origin were excluded because of commonality with other ethnic groups. The ETHNIC database has a positive predictive value (PPV) of 89.3% and



**Figure 1** Flow chart illustrating the study population cohort.

sensitivity of 50.4% to identify South Asian individuals, and PPV of 91.9% and sensitivity of 80.2% to identify people of Chinese origin. In addition, to address possible misclassification by the ETHNIC database, we linked immigration data from Immigration, Refugees and Citizenship Canada (IRCC)'s Permanent Residents Database<sup>8</sup> and defined ethnicity based on region of birth. The Ontario portion of IRCC data includes all immigrants arriving to Ontario after January 1, 1985 (people who immigrated prior to 1985 are misclassified as non-immigrants). As per World Bank region classification,<sup>9</sup> individuals were labelled as South Asian if they were born in India, Pakistan, Nepal, Bangladesh, Bhutan or Sri Lanka. Individuals were labelled as Chinese if born in China, Hong Kong or Taiwan. The Canadian-born children of immigrant mothers were identified by linking female immigrants to the MOMBABY database. MOMBABY links maternal and new-born records of hospital births from 1988 onward.<sup>10,11</sup>

We used the Ontario Crohn's and Colitis Cohort (OCCC) to identify all incident cases of IBD, and to distinguish CD from UC.<sup>12,13</sup> OCCC is a complete cohort of IBD patients living in Ontario from 1991 onwards. Validated lookback periods without health-care contacts for IBD were required to distinguish incident from prevalent cases (except for people born after April 1, 1991); 3 years for paediatric-onset IBD and 8 years for adult- or elderly-onset IBD. Therefore, the paediatric incident cohort started April 1, 1994; the adult/elderly incident cases starting April 1, 1999. The algorithm to identify children with IBD (aged 6mo to <18 years) was found to have a sensitivity of 89.6–91.1%, specificity >99.9%, PPV of 59.2–76.0% and negative predictive value (NPV) >99.9%.<sup>12</sup> In adults (aged 18 to <65 years) a sensitivity of 76.8–92.3%, specificity of 96.2–99.1%, PPV of 81.4% and NPV of 95.0%.<sup>13</sup> The algorithm in seniors (>65 years) had a sensitivity of 52.2–53.7%, specificity of 98.8–99.3%, PPV of 76.3%, and NPV of 98.0%.<sup>13</sup> IBD incident patients were further stratified as CD, UC or IBD type unclassifiable using a validated algorithm.<sup>12,13</sup>

## Exposure Ascertainment

We identified two ethnic groups using the above-mentioned databases, South Asian and Chinese, and the remaining population defined as the “general” cohort served as the comparative reference population. If ethnicity determined by immigration data differed from the ETHNIC database, ethnicity was assigned using country of birth from immigration data (Figure 1). We assessed the

degree of concordance in assigning ethnicity between the ETHNIC database and IRCC immigration data. The IRCC and ETHNIC databases were highly concordant among Chinese individuals (93.5% concordance), but less concordant among South Asians (37.7% concordance) (Supplementary Table 1).

## Outcome Ascertainment

The outcome of interest was the incident diagnosis of IBD, identified using the OCCC with the validated algorithms described above.

## Independent Variables (Confounders)

Multivariable models adjusted for the following a priori determined independent variables, identified as possible confounders using clinical knowledge and previous research: immigration status,<sup>12</sup> sex, neighbourhood income quintile at cohort entry<sup>14</sup> and Rurality Index of Ontario (RIO) at the time of cohort entry.<sup>15</sup> RIO is an ordinal variable measures the degree of rurality and consists of three broad components, measure of community population and density, measure of travel to nearest basic referral centre, and measure of travel time to nearest advanced centre.<sup>16</sup> The RIO is a normalised scale ranging from 0 to 100, with a score of 0 being the least rural.

## Statistical Analysis

Standardized incidence was calculated per 100,000 person years (PYs) of follow-up, with 95% confidence intervals (CI) based on gamma distribution, using age-appropriate standard populations. We used the Canadian Census data from 2016 to determine the annual intercensal population estimates.<sup>17</sup> To assess risk of IBD (including CD and UC subtypes), we compared incidence in ethnic groups. We calculated standardized incidence rate ratio (IRR) adjusted for age and sex with 95% CI using Poisson regression. We also determined adjusted IRR with 95% CI using negative binomial regression model, controlling for sex (female reference), immigration category (non-immigrant reference), income quintile (lowest income quintile as reference) and RIO rurality index at the time of cohort entry.

To determine the possible protective association of immigration status on the risk of IBD, we used multivariable models without controlling for immigration status (model 1) and controlling for immigration status (model 2). Age was categorized into three levels: i) 6 months to <18 years (paediatric); ii) 18 years to <65 years (adult); iii) ≥65 years (senior). Interaction between

age and the main exposure ethnicity (age\*ethnic) was included as an independent variable in model 3. If the interaction term was significant ( $p < 0.05$ ), the analysis was stratified by age group (model 4). We described normally distributed continuous variables as means and standard deviations (SD), and categorical variables were expressed as frequency and proportions. Statistical analyses were performed using Stata version 15 (StataCorp) and using SAS version 9.4 (SAS Institute, NC).

## Results

### Study Participants

Of the 16,230,638 residents of Ontario included in our cohort, 982,472 (6.1%) were South Asian and 764,397 (4.7%) Chinese. Over the follow-up period, 1644 South Asians and 444 Chinese developed IBD, and this accounted for 3.4% and 0.9% of total incident cases. See [Table 1](#) for the descriptive characteristics of the IBD cohort. Males predominated among South Asian and Chinese individuals with IBD comprising, respectively, 56% and 58% of these cohorts. The IBD South Asian cohort was younger relative

to the general and Chinese IBD cohorts. Non-immigrant South Asian people were diagnosed with IBD at  $30.3 \pm 18.7$ y, compared to  $39.1 \pm 18.7$ y in South Asian immigrants. There was no difference observed among immigrants and non-immigrants in the Chinese and general IBD cohorts ([Supplementary Table 2](#)). Less than 5% of the IBD patients in the general cohort were immigrants, compared to approximately 40% of South Asians, and 30% of Chinese IBD patients. No person was missing age or sex, and immigration status. Two percent of records were missing mean neighborhood income quintile and 0.5% were missing RIO score. These residents were removed from the analyses.

### Standardized Incidence Rates

Standardized incidence of IBD per 100,000 PYs in the general cohort was 24.7 (95% CI 24.4–25.0), compared with 14.6 (95% CI 13.7–15.5) in South Asians and with 5.4 (95% CI 4.8–5.9) in Chinese. The standardized incidence of CD per 100,000 PYs among the general cohort (10.6, 95% CI 10.4–10.7) was significantly higher than in the South Asians and Chinese populations (South Asians: 4.28, 95% CI 3.80–4.76; Chinese: 1.58, 95% CI 1.26–1.90). The standardized

**Table 1** Descriptive Characteristics of the IBD Population

	General Population	South Asian	Chinese
IBD incident cases	45,508	1644	444
Follow-up person-years	10.0±5.3	10.6±4.88	10.5±5.04
Male	21,959 (48.3%)	912 (55.5%)	259 (58.3%)
Age at diagnosis (y)	39.5±19.3	33.7±18.0	41.1±18.2
Age at diagnosis of immigrant (y)	37.5±15.6	39.1±15.3	41.3±14.7
Age at diagnosis of non-immigrant (y)	39.6±19.4	30.3±18.7	41.0±19.5
Age at diagnosis (y)			
<18y	6305 (13.9%)	377 (22.9%)	43 (9.7%)
18-<65y	33,831 (74.3%)	1173 (71.4%)	356 (80.2%)
≥65y	5372 (11.8%)	94 (5.7%)	45 (10.1%)
Rural	7525 (16.6%)	64 (3.9%)	14 (3.2%)
Income quintile			
1	8526 (19.2%)	519 (31.9%)	98 (22.5%)
2	8839 (19.9%)	415 (25.5%)	95 (21.8%)
3	8954 (20.1%)	320 (19.7%)	97 (22.2%)
4	9183 (20.7%)	240 (14.8%)	87 (20.0%)
5	8947 (20.1%)	131 (8.1%)	59 (13.5%)
Immigrant	1860 (4.1%)	642 (39.1%)	132 (29.7%)
Rurality Index 2008	11.2±17.9	1.7±5.0	2.4±8.2

**Notes:** Values are presented as N (%), mean ± standard deviation.

incidence of UC per 100,000 PYs among South Asians (9.56, 95% CI 8.83–10.3) and Chinese (3.54, 95% CI 3.06–4.02) was twice the rate of CD. The incidence rates and rate ratios by IBD type are reported in [Tables 2](#) and [3](#).

## Incidence in South Asians Compared with the General Population

The risk of IBD in South Asians was lower compared to the general population prior to adjusting for immigration status (model 1; adjusted IRR (aIRR) 0.73, 95% CI 0.69–0.76), but the same as the general population after adjusting for immigration in the model (model 2; aIRR 1.00, 95% CI 0.95–1.05) ([Table 4](#)). After adjustment for immigration status, only South Asian adults had a higher risk of IBD (aIRR 1.10, 95% CI

1.02–1.18), not children (0.98 95% CI 0.91–1.05) or seniors (0.38 95% CI 0.14–1.06) relative to the general population. Furthermore, immigration was significantly associated with a lower risk of both CD and UC ([Table 4](#) and [Supplementary Table 3](#)). The incidence of CD in South Asians was lower compared to the general population, irrespective of age (aIRR 0.66, 95% CI 0.60–0.76), whilst the risk of UC was higher in South Asian especially among children and adult South Asians (aIRR 1.47, 95% CI 1.34–1.61; children aIRR 1.36, 95% CI 1.24–1.49; adults aIRR 1.30, 95% CI 1.19–1.43). South Asians were more likely to develop UC than CD (aIRR 1.51, 95% CI 1.38–1.66) ([Table 5](#) and [Supplementary Table 6](#)). We observed a difference in IRR by age, and the incidence rate decreased with increasing age among South Asians relative to both the

**Table 2** Standardized Incidence Rate per 100,000 Person-Years (PYs) by Ethnicity (1999–2015) and IBD Type

	Number of Incident Cases	Total Population	PYs	Crude Incidence Rate per 100,000 PYs (95% CI)	Standardized Incidence Rate per 100,000 (PYs) (95% CI)
<b>Inflammatory bowel disease</b>					
General population	44,325	14,483,769	178,561,105	24.8 (24.6–25.1)	24.7 (24.4–25.0)
South Asian	1610	982,472	9,719,040	16.6 (15.8–17.4)	14.6 (13.7–15.5)
Chinese	439	764,397	8,393,123	5.2 (5.72–4.74)	5.4 (4.8–5.9)
<b>Crohn's Disease</b>					
General population	20,425	15,466,241	178,357,430	11.5 (11.3–11.6)	10.6 (10.4–10.7)
South Asian	493	982,472	9,708,882	5.08 (4.65–5.55)	4.28 (3.80–4.76)
Chinese	138	764,397	8,390,392	1.64 (1.37–1.92)	1.58 (1.26–1.90)
<b>Ulcerative Colitis</b>					
General population	21,635	15,466,241	178,372,216	12.1 (12.0–12.3)	12.9 (12.7–13.1)
South Asian	1027	982,472	9,713,445	10.6 (9.95–11.2)	9.56 (8.83–10.3)
Chinese	283	764,397	8,391,614	3.37 (3.00–3.79)	3.54 (3.06–4.02)

**Table 3** Standardized Incidence Rate Ratio by Ethnicity and IBD Type

	Inflammatory Bowel Disease		Crohn's Disease		Ulcerative Colitis	
	Crude IRR (95% CI)	Standardized IRR (95% CI)	Crude IRR (95% CI)	Standardized IRR (95% CI)	Crude IRR (95% CI)	Standardized IRR (95% CI)
South Asian vs general	0.69 (0.66–0.73)	0.59 (0.55–0.63)	0.46 (0.42–0.49)	0.41 (0.36–0.45)	0.91 (0.86–0.97)	0.74 (0.69–0.80)
Chinese vs general	0.21 (0.19–0.24)	0.22 (0.19–0.24)	0.15 (0.12–0.17)	0.15 (0.12–0.18)	0.28 (0.25–0.32)	0.28 (0.24–0.32)
South Asian vs Chinese	3.24 (2.92–3.60)	2.72 (2.40–3.09)	3.10 (2.58–3.74)	2.71 (2.15–3.41)	3.24 (2.84–3.69)	2.70 (2.31–3.15)

**Notes:** General the comparative reference population cohort.

**Abbreviation:** IRR, incidence rate ratio.

**Table 4** Incidence Rate Ratio Models of Inflammatory Bowel Disease, Crohn's Disease and Ulcerative Colitis, Comparing: South Asian Compared with General Population, Chinese with General and South Asian with Chinese

	Inflammatory Bowel Disease		Crohn's Disease		Ulcerative Colitis	
	IRR (95% CI)	SE	IRR (95% CI)	SE	IRR (95% CI)	SE
<b>South Asian (Ref: General)</b>						
Model 1 (-immigration status) <sup>†</sup>	0.73 (0.69–0.76)	0.02	0.48 (0.44–0.52)	0.02	0.95 (0.89–1.01)	0.03
Model 2 (+ immigration status)	1.0 (0.95–1.05)	0.03	0.70 (0.64–0.77)	0.03	1.25 (1.17–1.33)	0.04
Model 3 (*agegp)	1.03 (0.96–1.10)	0.04	0.66 (0.60–0.76)	0.04	1.47 (1.34–1.61)	0.07
Model 4a (<18y)	0.98 (0.91–1.05)	0.04	0.66 (0.58–0.74)	0.04	1.36 (1.24–1.49)	0.07
Model 4b (18–<65y)	1.10 (1.02–1.18)	0.04	0.77 (0.67–0.89)	0.06	1.30 (1.19–1.43)	0.06
Model 4c (>65y)	0.38 (0.14–1.06)	0.20	0.19 (0.02–1.64)	0.21	0.61 (0.18–2.02)	0.37
<b>Chinese (Ref: General)</b>						
Model 1 (-immigration status) <sup>†</sup>	0.22 (0.20–0.24)	0.01	0.15 (0.13–1.18)	0.01	0.28 (0.25–0.32)	0.02
Model 2 (+immigration status)	0.26 (0.24–0.29)	0.01	0.19 (0.16–0.23)	0.02	0.33 (0.29–0.37)	0.02
Model 3 (*agegp)	0.24 (0.20–0.28)	0.02	0.21 (0.17–0.26)	0.02	0.28 (0.23–0.35)	0.03
Model 4a (<18y)	0.23 (0.20–0.27)	0.02	0.20 (0.16–0.26)	0.02	0.27 (0.21–0.33)	0.03
Model 4b (18–<65y)	0.30 (0.26–0.33)	0.02	0.18 (0.14–0.23)	0.02	0.38 (0.33–0.44)	0.03
Model 4c (>65y)	0.22 (0.09–0.52)	0.10	0.19 (0.04–0.88)	0.15	0.27 (0.09–0.81)	0.15
<b>South Asian (Ref: Chinese)</b>						
Model 1(-immigration status) <sup>†</sup>	3.37 (3.03–3.75)	0.18	3.15 (2.61–3.81)	0.30	3.40 (2.98–3.89)	0.23
Model 2 (+immigration status)	3.73 (3.35–4.15)	0.20	3.52 (2.90–4.24)	0.34	3.76 (3.29–4.30)	0.26
Model 3 (*agegp)	4.29 (3.62–5.08)	0.37	3.26 (2.45–4.09)	0.41	5.19 (4.01–6.57)	0.63
Model 4a (<18y)	4.25 (3.58–5.04)	0.37	3.19 (2.46–4.13)	0.42	5.13 (4.04–6.51)	0.62
Model 4b (18–<65y)	3.54 (3.07–4.08)	0.26	3.76 (2.82–5.02)	0.55	3.38 (2.85–4.01)	0.29
Model 4c (>65y)	2.24 (0.61–8.19)	1.48	1.35 (0.12–15.0)	1.66	3.63 (0.51–25.9)	3.64

**Notes:** All models adjusted for covariates: immigration status <sup>†</sup>exclusion of immigration status from model 1), male (female as reference), neighbourhood income quintile (lowest income quintile as reference) and RIO2008. \*Agegp interaction term.

**Abbreviations:** CI, confidence intervals; IRR, incidence rate; SE, standard error.

**Table 5** Incidence Rate Ratio Models of Ulcerative Colitis Relative to Crohn's Disease

	South Asian General (REF)		Chinese General (REF)		South Asian Chinese (REF)	
	IRR (95% CI)	SE	IRR (95% CI)	SE	IRR (95% CI)	SE
Model 1 (-immigration status)	1.25 (1.17–1.33)	0.04	1.24 (1.09–1.39)	0.07	1.00 (0.88–1.15)	0.07
Model 2 (+immigration status)	1.19 (1.12–1.28)	0.04	1.20 (1.06–1.35)	0.07	0.99 (0.87–1.14)	0.07
Model 3 (*agegp)	1.51 (1.38–1.66)	0.07	1.09 (0.87–1.36)	0.12	1.36 (1.08–1.73)	0.16

**Notes:** All models adjusted for covariates: immigration status <sup>†</sup>exclusion of immigration status from model 1), male (female as reference), neighbourhood income quintile (lowest income quintile as reference) and RIO2008. \*Agegp interaction term.

**Abbreviations:** CI, confidence intervals; IRR, incidence rate; SE, standard error; REF, reference group.

general and Chinese population (Figure 2 and Supplementary Figures 1, 2, 5, and 6).

## Incidence in Chinese population Compared with the General Population

The risk of IBD was much lower in Chinese population, irrespective of age, compared to the general population (aIRR 0.24, 95% CI 0.20–0.28). This lower risk was

similar in UC (aIRR 0.28, 95% CI 0.23–0.35) and CD (aIRR 0.21 95% CI 0.17–0.26) (Table 4 and Supplementary Table 4). Immigration status did not significantly change the aIRR in the models (comparing model 1 with model 2). The IRR stratified by age and sex are demonstrated in Figure 2 (Supplementary Figures 3 and 4), with no noticeable difference in IRR by age.

## Incidence in South Asian Population Compared with the Chinese Population

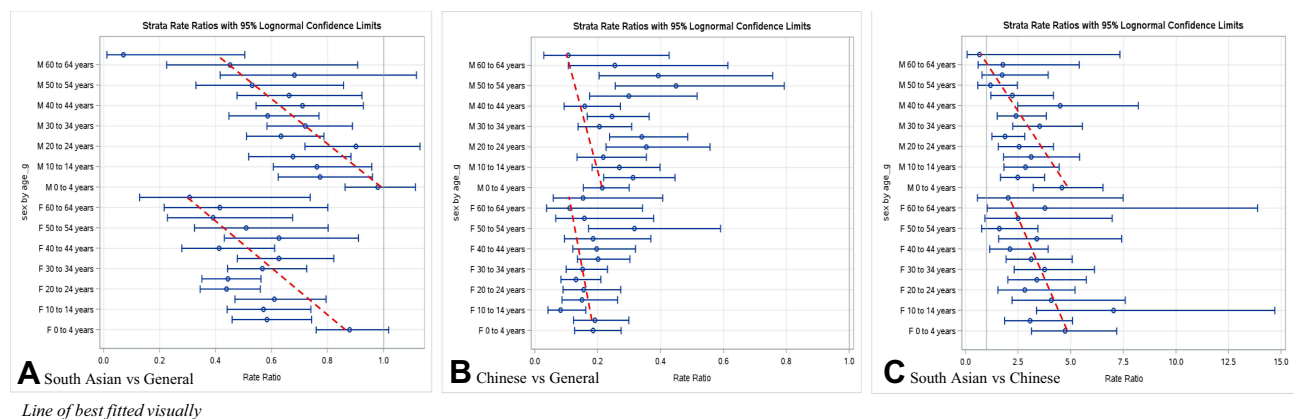
The risk of IBD among South Asian children and adults was approximately four times higher than the Chinese population, irrespective of IBD type (Table 4 and Supplementary Table 5). South Asians had a greater risk of ulcerative colitis (vs CD) compared to Chinese population (IRR 1.36, 95% CI 1.08–1.73) (Table 5), and the risk of IBD (CD/UC) among South Asian relative to Chinese decreased with age (Figure 2 and Supplementary Figures 5 and 6).

## Discussion

In this population-based study, the risk of developing IBD among South Asian people was comparable to the general population after adjusting for immigration status. This was not the case for Chinese residents, who had a significantly lower risk of IBD in both immigrants and non-immigrants. Notably, after adjustment for immigration status and other confounders, the risk of UC in South Asians was 1.5-fold higher than the general population. There was a male predominance in both the Chinese and South Asian IBD cohorts compared to the general population cohort. We also observed a distinct age-risk relationship in South Asians only, with higher relative incidence in younger people. Furthermore, South Asian and Chinese people were more likely to develop UC relative to CD compared to the general population. Our study supports the hypothesis that the likelihood of IBD, specifically UC, among the South Asian population is greater than in the Chinese population, and like the high incidence rates of IBD described in the general Canadian population.

The landscape of IBD is evolving; in the Western world, incidence is stabilizing and regions transitioning into

a compounding prevalence stage, whilst newly industrialised countries entering acceleration in incidence stage, associated with rising incidence and low prevalence.<sup>2,18</sup> This is particularly evident in South Asia, with countries such as India approaching the incidence of IBD comparable to the West.<sup>2</sup> The present study further supports the notion that the risk of IBD increases in certain migrant groups from countries with lower IBD prevalence once they arrive to higher prevalence countries such as Canada, USA and the United Kingdom.<sup>6,19–21</sup> The predominance of UC observed in both South Asian and Chinese IBD populations is consistent with other population-based studies from the Asia-Pacific region.<sup>22</sup> The comparatively lower CD incidence rates may be attributed to the lack of a genotypic association. CD-associated polymorphisms in the NOD2/CARD15 gene are strongly associated with ileal CD,<sup>23</sup> but the higher prevalence of these common risk alleles of European origin has not been widely observed in South Asians<sup>24</sup> and Chinese patients.<sup>25</sup> Likewise, population studies in the United Kingdom<sup>19,20</sup> have observed a higher risk of UC among adult South Asians. In addition, using self-reported ethnicity in a prospective Canadian pediatric inception cohort study, we recently observed a predominance of UC in South Asian children and adolescents with IBD.<sup>26</sup> We previously demonstrated that earlier age of immigration was associated with an increased risk of IBD, with risk increasing by 14% for every younger decade of life at immigration.<sup>6</sup> Similarly, in our cohort, South Asians born in Canada with IBD presented at an earlier age relative to South Asian immigrants and the Chinese and general populations. These findings support that earlier exposure to the Canadian environment increases the risk of IBD and moreover UC, in this population.



**Figure 2** Inflammatory bowel disease unadjusted incidence rate ratio stratified by age and sex; [A] South Asian compared with general population; [B] Chinese compared with “general” population; [C] South Asian compared with Chinese population.

It has been speculated that early exposure to environmental risk factors modifies the risk of developing IBD in genetically susceptible individuals.<sup>27,28</sup> Notably, the emergence of IBD in Asian and Asian-Pacific countries associated with Westernisation signifies the important role of environmental factors.<sup>2,22</sup> A recent meta-analysis of observational studies identified nine risk (smoking, urban living, vitamin D deficiency) and seven protective environmental factors (breastfeeding, tea, physical activity), with moderate to high epidemiologic evidence of association.<sup>27</sup> However, evidence of association does not equate to causality and factors such as serum vitamin levels and microorganisms may be a consequence of reverse causation. The degree to which, and pathophysiologic mechanism by which, these environmental exposures contribute to risk of developing IBD remains to be elucidated. The relative contribution of environmental risk factors may vary according to the population studied. In our study, the risk of IBD among the Chinese population remained low even after adjusting for immigration, suggesting that exposure to the Canadian environment, even in people born in Canada, may not trigger IBD in people of Chinese origin. Protective genetic or microbiome factors may mitigate such environmental effects. These findings highlight the heterogeneity of the disease and the complex interplay of environmental, microbial, immunological and genetic factors, and future research should further assess the interplay of these factors among various ethno-cultural groups.

The strengths of this study include its large sample size and population-based study design. Linkage of multiple health administrative databases allowed us to calculate the incidence of IBD within ethnic groups in Ontario, and to adjust for known confounders. The use of health administrative data presents some limitations, including risk of misclassification bias, which could result from miscategorising people as having or not having IBD. However, we used validated algorithms in our study to identify patients with IBD, differentiate incident from prevalent cases, and classify IBD patients as having CD or UC.<sup>12,13</sup> The IBD algorithms were not specifically validated in immigrants and we may have differentially misclassified people in these groups as having or not having IBD based on their health services utilisation patterns. However, we previously reported that health services utilisation was not different among immigrants with IBD compared to non-immigrants, reducing the risk of differential misclassification.<sup>29</sup>

Another limitation of this study is the assignment of South Asian ethnicity based on a surname-based algorithm, which was an excellent PPV but a sensitivity of 50.4%.<sup>7</sup> The lower sensitivity was likely due to the exclusion of South Asian people with Muslim or European surnames, as to avoid misclassification. To overcome this weakness, we linked immigration and birth data to assign ethnicity. Immigrants from South Asia or China/Hong Kong were classified as being of South Asian and Chinese ethnicity, respectively, even when the surname algorithm did not classify them as such. The children of immigrant mothers from those regions were classified with the same approach. However, immigration data were only available from 1985, and include only immigrants whose first place of landing was Ontario. Therefore, there is still the risk of misclassification. In our study, South Asians comprised 6.1% and Chinese 4.7% of the entire Ontario population, which was analogous to the 2006 and 2016 Canadian census (South Asian 6.6% and 8.7%, Chinese 4.7% and 5.7%, respectively).<sup>4,30</sup> Finally, Ontario health administrative data does not link records of fathers to their children, and therefore we were uncertain of the fathers' immigration status. However, the overall rate of intermarriage among minority populations in Canada is low (13.0% in South Asians, 19.4% in Chinese).<sup>31</sup>

In conclusion, we found that the incidence of IBD among South Asians living in Canada was comparable to the high incidence seen in other Canadians, and significantly higher than incidence rates seen in first-generation immigrants to Canada. Rates in South Asians were much higher than in the Chinese population, even when they were born in Canada. The strong protective effect of immigration to Canada implies that environmental factors to which non-immigrant Canadians of South Asian descent are exposed increase the risk of this immune mediated inflammatory disease. Further research is warranted to understand the pathophysiological reasons for these epidemiological findings, and to understand the health-care needs of the growing numbers of South Asian people with IBD.

## Data Sharing Statement

The data underlying this article was accessed from ICES, which is funded by the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The analysis undertaken in this study is based on data and information compiled and provided by: MOH, and the Canadian Institute for Health Information (CIHI). Data sharing is



governed under a data sharing agreement between ICES and the Ministry of Health and Long-term Care. The derived data generated in this research will be shared on reasonable request to the corresponding author following approval by ICES.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

No conflicts to declare: Jasbir Dhaliwal, Emily Herrett, Meltem Tuna, Sanjay Murthy, Baiju Shah.

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matters unrelated to a medication used to treat inflammatory bowel disease. Dr. Benchimol also acted as a consultant for McKesson Canada. The authors report no other conflicts of interest in this work. The Data Accessed Complies with Relevant Data Protection and Privacy Regulations.

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