

BMJ Open Prevalence of positive coeliac disease serology and HLA risk genotypes in a multiethnic population of adults in Canada: a cross-sectional study

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ABSTRACT

Objectives Coeliac disease (CD) is a complex autoimmune disorder with known genetic risk factors. Approximately 1% of individuals of European ancestry have CD, but the prevalence among different ethnicities living in Canada remains unknown. The objective of the present study was to determine the prevalence of positive CD serology in a population of Canadian adults living in Toronto, and to determine whether the prevalence of CD seropositivity and predisposing human leucocyte antigen (HLA)-DQ2/DQ8 risk genotypes differ between major ethnocultural groups.

Design Cross-sectional screening study of participants from the Toronto Nutrigenomics and Health and the Toronto Healthy Diet studies.

Setting University campus and households across Toronto, Canada.

Participants: free-living Adults (n=2832) of diverse ethnocultural backgrounds.

Main outcome measures Prevalence of positive CD serology was determined by screening for antitissue transglutaminase antibodies in individuals with predisposing HLA-DQ2/DQ8 genotypes. HLA genotypes were determined using six single nucleotide polymorphisms in the HLA gene region.

Results Of the 2832 individuals screened, a total of 25 (0.88%; 95% CI 0.57% to 1.30%) were determined to have positive CD serology. The majority of seropositive CD cases were undiagnosed (87%). Prevalence was highest among Caucasians (1.48%; 95% CI 0.93% to 2.23%), and similar in those of 'Other' (0.74%; 95% CI 0.09% to 2.63%) or 'Unknown' (0.43; 95% CI 0.01% to 2.36%) ethnicity. No cases of positive CD serology were identified among East Asian or South Asian individuals. East Asians had a lower prevalence of HLA risk genotypes than Caucasians and South Asians ($p < 0.005$).

Conclusions The prevalence of positive CD serology among Canadian adults living in Toronto is likely ~1%, with 87% of cases being undiagnosed. These findings suggest the need for better screening in high genetic risk groups.

Trial registration number NCT00516620; Post-results.

INTRODUCTION

Coeliac disease (CD) is an autoimmune disorder with defined genetic risk factors.

Strengths and limitations of this study

- This is the first study to screen for coeliac disease (CD)-associated antibodies in a population of adults living in Canada.
- There was representation of three major ethnic groups living in Canada and a wide age range across study populations included.
- There were low numbers of individuals in some ethnocultural groups examined, and estimates of the prevalence of positive CD serology in these groups should be interpreted with caution.
- Individuals with positive CD serology did not undergo a confirmatory biopsy for a definitive CD diagnosis.

Human leucocyte antigen (HLA)-DQ2 or HLA-DQ8 alleles are considered necessary for the development of CD as virtually all affected individuals possess these genetic variants.^{1–3} Dietary exposure to gluten, a protein found in wheat, barley and rye, triggers adverse autoimmune reactions in affected individuals. Damage to the intestinal mucosa, which is characteristic of CD, can ultimately result in nutrient malabsorption, and the only effective treatment to date is strict adherence to a gluten-free diet.⁴ Diagnosis of CD is made using a combination of serological tests and a confirmatory biopsy, which remains the gold standard.⁵ Individuals typically undergo screening for IgA antitissue transglutaminase (anti-tTG) or antiendomysial antibodies.⁶ Antibodies in the IgG class are assessed in cases of IgA deficiency,^{6,7} which can occur in up to 5% of individuals with CD.⁸ Symptoms of CD may include diarrhoea, steatorrhoea, malnutrition and iron-deficiency anaemia, although adults typically only display some symptoms of gastrointestinal discomfort and many may be relatively asymptomatic.^{4,9} If untreated, individuals with CD may be at an increased

risk for various nutrient deficiencies,¹⁰ osteoporosis,¹¹ infertility,¹² certain gastrointestinal lymphomas¹³ and overall mortality.¹⁴

Approximately 1% of individuals in the USA and many European populations are affected by CD.^{14–19} Of particular concern is that the prevalence of CD has been shown to be on the rise.^{14 18 20 21} The prevalence of CD in East Asian populations is thought to be much lower than in Caucasians^{18 22}; however, emerging evidence suggests that CD may be increasingly prevalent in China,^{23 24} particularly in regions with higher wheat consumption.²⁴ CD has been shown to be more common in individuals of South Asian descent.^{5 25–27} Variation in the prevalence of HLA-DQ2/DQ8 risk alleles is thought to explain some of the regional variation in CD prevalence^{5 26}; however, the extent to which such variation influences the prevalence of CD in immigrant populations is unclear. Furthermore, the prevalence of CD among Canadian adults, including those of various ethnocultural backgrounds, remains unknown. The objective of this study was to determine the prevalence of positive CD serology in a population of Canadian adults living in Toronto, and to determine whether the prevalence of CD seropositivity and predisposing HLA-DQ2/DQ8 risk genotypes differ between major ethnocultural groups.

METHODS

Study populations

Toronto Nutrigenomics and Health study

The Toronto Nutrigenomics and Health (TNH) study is a cross-sectional cohort of young adults aged 20–29 years living in Toronto, Canada. Subjects (n=1639) were recruited from the University of Toronto campus through postings and advertisements between October 2004 and December 2010. Pregnant or breastfeeding women were excluded from the study. All individuals completed a general health and lifestyle questionnaire, had anthropometric measurements taken, and provided a fasting blood sample for various biomarker assessments and for DNA isolation. The ethnocultural background of each subject was ascertained by self-report. Individuals were classified as either Caucasian (European, Middle Eastern or Hispanic), East Asian (Chinese, Japanese, Korean, Filipino, Vietnamese, Thai or Cambodian), South Asian (Bangladeshi, Indian, Pakistani or Sri Lankan) or Other (Aboriginal Canadians, Afro-Caribbean or individuals belonging to two or more distinct ethnocultural groups).²⁸ A total of 1620 subjects (1103 women and 517 men) with available plasma samples were included in the study, which was approved by the Research Ethics Board at the University of Toronto.

Toronto Healthy Diet study

The Toronto Healthy Diet (THD) study is a randomised controlled trial designed to investigate whether increased consumption of fruits, vegetables and whole grains would lead to a reduction in body weight and improvement

in biomarkers of obesity-related chronic disease.²⁹ The study protocol was registered with ClinicalTrials.gov (NCT00516620) and was approved by the Research Ethics Boards at the University of Toronto and St Michael's Hospital. Households in the Toronto region with at least one person having a body mass index ≥ 25 kg/m² were recruited into the study through postings and advertisements. Individuals with chronic conditions, including diagnosed CD, were excluded from the study. A total of 1245 adults 18–82 years of age provided baseline data, which included anthropometric measurements and a fasting blood sample for biomarker assessment and DNA isolation. The ethnocultural background of participants was assessed by self-report, and individuals were classified into the same groups described above for the TNH study. An additional 'Unknown' ethnocultural group was included for the THD study, where data on ethnicity were missing (n=234). All 1212 individuals (901 women and 311 men) with baseline plasma samples available were included in the study.

Genotyping

HLA genotyping was performed using TaqMan allelic discrimination assays (Applied Biosystems) at the Analytical Genetics Technology Centre at the Princess Margaret Hospital, University Health Network, Toronto, Canada. Genotyping was conducted for six single nucleotide polymorphisms (SNPs) in the HLA region (rs7454108, rs2395182, rs7775228, rs4713586, rs2187668 and rs4639334), which collectively determines the presence of HLA-DQ2/DQ8 alleles associated with CD.³⁰ Subjects were categorised into risk groups for CD based on a previously established HLA gradient.³ Subjects with DQA1*0501-DQB1*0201 (DQ2.5), DQA1*0301-DQB1*0302 (DQ8) or DQA1*0505-DQB1*0301/DQA1*0201-DQB1*0202 (DQ2.2/DQ7) were considered to be at 'elevated risk' for CD compared with the general population.^{1 3} A total of 2832 subjects underwent genotyping and were included in all analyses.

CD serology

Anti-tTG antibodies from plasma samples stored at -80°C were measured using human-recombinant tTG ELISA. Only subjects classified as 'elevated risk' for CD based on their HLA-DQ genotype plus all those with at least one copy of DQA1*0201-DQB1*0202 (DQ2.2) had their plasma analysed (n=1555), since virtually all individuals with CD possess such alleles.³ Initially, samples were analysed using dual-isotope transglutaminase kits screening for tTG antibodies in both the IgA class and IgG class (product no ORG540S; Orgentec Diagnostika, Main, Germany). This was done to account for individuals with selective IgA deficiency,³¹ the primary cause of false-negative test results with tTG IgA screening.³² The threshold for a positive test result was ≥ 15 U/mL. All samples that tested positive were then analysed using a separate kit for tTG IgA (product no ORG540A, Orgentec Diagnostika).

The threshold for a positive test result for tTG IgA was ≥ 10 U/mL. Individuals who tested positive for tTG IgA antibodies were considered to have positive CD serology. Individuals who tested negative for tTG IgA were screened for IgA deficiency using ELISA (product no CSB-E07985h, Cusabio Biotech, Wuhan, China). Individuals with IgA deficiency (total IgA < 7 mg/dL)³³ were then screened using a separate kit for tTG IgG (product no ORG540G; Orgentec Diagnostika). Those with IgA deficiency and positive tTG IgG (≥ 10 U/mL) were considered to have positive CD serology. Equivocal results were assigned if the dual-isotope screen was positive, but individuals subsequently tested negative for tTG IgA antibodies and were IgA-sufficient. Such cases are likely driven by tTG IgG, and screening for such antibodies is not recommended due to the low diagnostic utility of tTG IgG in IgA-sufficient populations.^{32,34} Individuals in the TNH population who reported having been diagnosed with CD on the general health and lifestyle questionnaire were also considered to have positive CD serology.

Statistical analysis

Statistical analyses were conducted using Statistical Analysis Software V.9.2. For all analyses, the α -error was set at 0.05 and reported p values are two-sided. Continuous variables were log_e-transformed or square root-transformed to improve normality where necessary. Although reported p values are from models using transformed variables, means and measures of spread for such variables are reported in their untransformed state to facilitate interpretability. Binomial 95% CIs (Clopper-Pearson) were calculated for all dichotomous variables.

Subject characteristics between the two study populations were assessed using analysis of covariance and χ^2 tests for continuous and categorical variables, respectively. Fisher's exact test was used to determine whether there were differences in the frequency of the HLA-DQ2/DQ8 elevated-risk genotypes between ethnocultural groups. All possible pairs of ethnocultural groups were compared. The Bonferroni adjustment for multiple testing was used to account for the multiple pairwise comparisons ($p < 0.005$, calculated based on 10 pairwise comparisons and $\alpha = 0.05$). Differences in the prevalence of positive CD serology between the two study populations were assessed using exact logistic regression adjusted for sex and ethnicity. Exact logistic regression adjusted for ethnicity and study population was also used to assess differences in the proportion of men and women with elevated tTG antibodies.

RESULTS

Subject characteristics for both study populations are shown in table 1. Differences ($p < 0.05$) in age, sex, ethnocultural status, anthropometric measurements, blood pressure, blood glucose and lipid profiles were observed between study populations.

Table 1 Subject characteristics for TNH and THD study populations

	TNH study	THD study	p
Subjects (n)	1620	1212	
Age (year)	22.7 \pm 0.06*	44.7 \pm 0.36	<0.0001
Sex (n (%))			0.0003
Female	1103 (68)	901 (74)	
Male	517 (32)	311 (26)	
Ethnicity (n (%))			<0.0001
Caucasian	769 (47)	721 (59)	
East Asian	560 (35)	54 (4)	
South Asian	173 (11)	49 (4)	
Other	118 (7)	154 (13)	
Unknown	–	234 (19)	
BMI (kg/m ²)	22.9 \pm 0.09	32.5 \pm 0.17	<0.0001
Waist circumference (cm)	74.4 \pm 0.23	102.1 \pm 0.42	<0.0001
Systolic blood pressure (mm Hg)	114 \pm 0.29	115 \pm 0.36	<0.0001
Diastolic blood pressure (mm Hg)	69 \pm 0.20	73 \pm 0.26	<0.0001
Glucose (mmol/L)	4.79 \pm 0.01	4.91 \pm 0.02	<0.0001
Cholesterol			
Total (mmol/L)	4.26 \pm 0.02	5.07 \pm 0.03	0.02
HDL (mmol/L)	1.54 \pm 0.01	1.27 \pm 0.01	<0.0001
LDL (mmol/L)	2.28 \pm 0.02	3.23 \pm 0.02	<0.0001
Total:HDL cholesterol	2.91 \pm 0.02	4.23 \pm 0.04	<0.0001

*Mean \pm SE (all such values). Differences between study populations were assessed using χ^2 tests for categorical variables and ANCOVA-adjusted for age, sex, BMI and ethnicity for continuous variables.

ANCOVA, analysis of covariance; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; THD, Toronto Healthy Diet; TNH, Toronto Nutrigenomics and Health.

HLA-DQ genotypes

The overall prevalence of elevated-risk HLA-DQ2/DQ8 genotypes across both study populations was 38.4% (95% CI 36.6% to 40.2%). The proportion of individuals with elevated-risk HLA-DQ genotypes in each ethnocultural group is shown in figure 1. Caucasians and South Asians had a higher proportion of elevated-risk HLA genotypes than East Asians ($p < 0.005$), while individuals in the 'Other' and 'Unknown' groups had an intermediate prevalence of such alleles. A breakdown of all HLA-DQ subcategories by ethnocultural group is shown in online supplementary figure S1. Generally, the presence of higher risk HLA-DQ risk alleles was increasingly rare as their associated CD risk increased across all ethnocultural groups.

Anti-tTG antibodies

A total of 46 individuals tested positive on the initial dual-isotope tTG-IgA/IgG screen. Of these individuals,

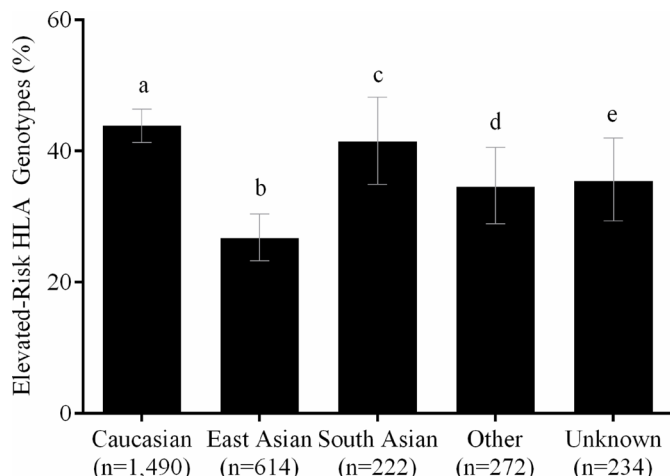


Figure 1 Prevalence of coeliac disease-associated elevated-risk HLA genotypes across ethnocultural groups. Elevated-risk genotypes include DQA1*0501-DQB1*0201 (DQ2.5), DQA1*0301-DQB1*0302 (DQ8) or DQA1*0505-DQB1*0301/DQA1*0201-DQB1*0202 (DQ2.2/DQ7). Differences in the prevalence of elevated-risk genotypes between groups were compared using Fisher's exact test. All pairs of ethnocultural groups were compared, and a Bonferroni correction was applied to account for the multiple pairwise tests ($p < 0.005$, calculated based on 10 pairwise comparisons and $\alpha = 0.05$). a versus b, a versus d, b versus c: $p < 0.005$; $p > 0.005$ for all other comparisons. Error bars represent 95% CI. HLA, human leucocyte antigen.

22 tested positive for tTG IgA antibodies and were considered to have positive CD serology. Of the individuals who tested positive on the dual-isotope screen but negative for tTG IgA, one individual was found to be IgA-deficient (total IgA < 7 mg/dL) and tested positive for tTG IgG antibodies. This individual was also considered to have positive CD serology. Two additional individuals who reported having been diagnosed with CD were also considered to have positive CD serology. Both of these individuals possessed HLA-DQ2 and/or HLA-DQ8 genotypes but were tTG-negative, likely due to their adherence to a strict gluten-free diet. In total, 25 individuals were identified with positive CD serology, which translates to an overall prevalence of 1:114 (0.88%; 95% CI 0.57% to 1.30%). In the TNH study population, 13 out of 15 (87%) cases were identified exclusively through serology and did not report having been diagnosed with CD in the health questionnaire. These likely represent cases of undiagnosed CD. Estimates on the ratio of undiagnosed to diagnosed cases of CD were not available for the THD study population since a diagnosis of CD would have excluded individuals from the study. Estimates for the prevalence of CD across ethnocultural groups are shown in table 2. The majority of individuals with positive CD serology were Caucasian. No cases of positive serology were identified among East Asian or South Asian individuals, while a limited number of cases were identified among those of 'Other' and 'Unknown' ancestry. The prevalence did not differ between the TNH population (0.93%; 95% CI 0.52% to 1.52%) and the THD population (0.83%;

Table 2 Prevalence of positive coeliac disease (CD) serology across ethnocultural groups*

Ethnocultural group	Cases (n)	Prevalence (% (95% CI))
Total population (n=2832)	25	0.88 (0.57 to 1.30)
Caucasian (n=1490)	22	1.48 (0.93 to 2.23)
East Asian (n=614)	0	–
South Asian (n=222)	0	–
Other (n=272)	2	0.74 (0.09 to 2.63)
Unknown (n=234)	1	0.43 (0.01 to 2.36)

*Cases of CD were determined by measuring levels of antitissue transglutaminase (anti-tTG) IgA antibodies and previous diagnosis. tTG IgG antibodies were assessed in cases of IgA deficiency.

95% CI 0.40% to 1.51%) after adjusting for sex and ethnicity ($p = 0.32$). There was no difference in the prevalence between men (0.72%; 95% CI 0.27% to 1.57%) and women (0.95%; 95% CI 0.57% to 1.48%) after adjusting for study population and ethnicity ($p = 0.74$). The proportion of individuals with positive CD serology by subcategory of HLA risk is shown in figure 2. The proportion of individuals with positive serology tended to increase with increasing predefined HLA risk status,³ although differences between risk groups were not statistically significant ($p > 0.05$).

DISCUSSION

CD represents a common autoimmune condition in North America and Europe.³⁵ The prevalence of CD is known to vary globally and is thought to be particularly rare in certain regions, notably in Asia.^{5 18 26} Differences

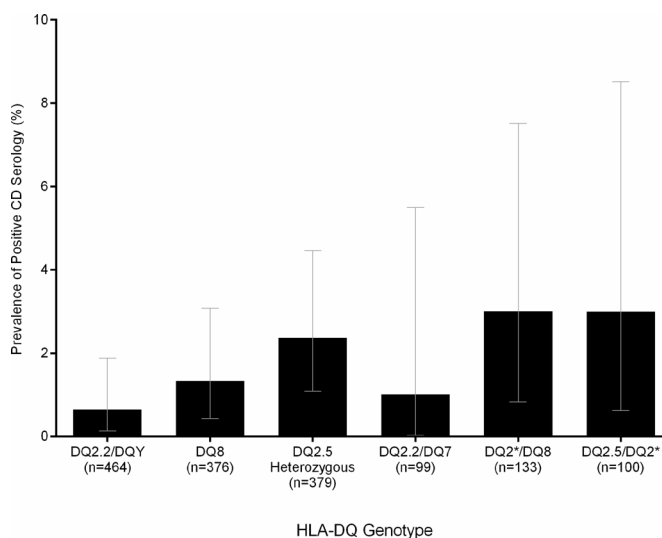


Figure 2 Prevalence of elevated tissue transglutaminase antibodies by CD-associated HLA-DQ risk category. HLA risk groups (increasing risk from left to right) modified from previously established risk gradient.³ Error bars represent 95% CIs. DQY, DQ2.2 or non-DQ2/DQ8 type; DQ8, DQ8 heterozygotes and homozygotes; DQ2*, DQ2.2 or DQ2.5 type. CD, coeliac disease; HLA, human leucocyte antigen.

in the prevalence of HLA variants conferring susceptibility to CD partially explain variability in the prevalence of CD observed between nations^{18 26}; however, it is unclear whether such variation plays a role in the development of CD in individuals of different ethnicities living in North America. Furthermore, there is a notable lack of screening studies assessing the prevalence of CD in individuals from diverse ethnocultural backgrounds living in Canada. To our knowledge, the present study is the first to screen for CD-associated antibodies in a population of Canadian adults. We found the prevalence of positive CD serology among ethnoculturally diverse Canadians living in Toronto to be 0.88% (95% CI 0.57% to 1.30%), which is similar to estimates in Europe and the USA.^{14–19} Furthermore, 87% of possible CD cases were undiagnosed, which is consistent with commonly reported figures of about 85%,^{9 35 36} and consistent with findings from the Canadian Celiac Association Health Survey indicating an average delay in diagnosis of ~12 years after the onset of symptoms.³⁷ Caucasians comprised the majority of cases with positive CD serology, while no individuals of East Asian or South Asian descent had positive serology or a previous diagnosis. Compared with Caucasians, East Asians had a lower prevalence of HLA-DQ elevated-risk genotypes, while South Asians and Caucasians had a similar prevalence of such genotypes.

Strengths of the present study include its large sample size and representation of three major ethnic groups living in Canada. Furthermore, individuals were not selected based on suspicion of CD, and estimates of the prevalence of undiagnosed CD are likely not inflated compared with the general population. There are, however, some notable limitations. There were low numbers of individuals in some ethnocultural groups examined, and estimates of the prevalence of positive CD serology in these groups should be interpreted with caution. Furthermore, while the populations included were from Toronto, Canada's largest metropolis, the results may not be generalisable to all Canadian adults. There was an over-representation of women in the study population due to the self-selected nature of the study participants. Additionally, although human-recombinant tTG IgA assays have a sensitivity and specificity of 98% for CD on average,³² subjects with positive serology did not undergo a confirmatory biopsy for a definitive diagnosis of CD. This also precluded the assessment of CD severity in cases of positive serology. The HLA genotyping methodology employed in the present study was optimised for European populations, and it is possible that other, currently unidentified tag SNPs in the HLA region serve as alternate markers for the predisposing HLA-DQ genotypes required for the development of CD in non-European populations.³⁰ Finally, while 13% of likely CD cases in the TNH population were previously diagnosed, we were unable to assess cases of diagnosed CD in the THD cohort since such individuals would have been excluded from the study. However, if a similar ratio of diagnosed to undiagnosed cases between study populations is assumed, this would equate to an additional

two individuals with clinically diagnosed CD in the THD cohort, increasing the prevalence of positive CD serology to 27 out of 2834 (0.95%; 95% CI 0.63% to 1.38%) in our multiethnic population of Canadian adults.

CD is known to vary by ethnicity and has historically been considered to primarily affect Caucasians.^{5 38} Our findings indicate that Caucasians are among the highest risk ethnocultural groups for CD in Canada. In contrast, CD is rare in East Asia,^{18 22} although case reports have been previously documented in East Asians living in Canada.³⁹ This is consistent with our findings that CD is rare in East Asians, and this is partly due to the lower prevalence of HLA-DQ2/DQ8 risk alleles. Conversely, we found that the prevalence of risk alleles in South Asians is similar to the prevalence of such alleles in Caucasians. This suggests that CD may occur in South Asians at a frequency that approaches that of Caucasians. Indeed, although we did not identify any South Asians with positive CD serology in the present study, screening studies in South Asian populations around the world suggest that CD may affect individuals at frequencies similar to Caucasians.^{25 40–42}

Demographic characteristics of individuals with CD are of considerable interest. We observed no difference in the prevalence of positive CD serology between men and women. While it has been reported that more women are diagnosed with CD,⁴ our results are in agreement with other screening studies that report similar rates of CD between sexes.^{15 36} Screening studies have also suggested that the prevalence of CD is similar across age groups.^{14 15 19 36} In agreement with these findings, we observed no significant difference in the prevalence of positive CD serology between the TNH and THD cohorts, populations with average ages of 23 and 45 years, respectively. Finally, while rare in the general population, IgA deficiency occurs more often in CD,³² affecting roughly 3%–5% of individuals with this condition.⁸ Consistent with these estimates, we found that 1 out of 23 (4.3%) individuals with positive CD serology was IgA-deficient.

We observed a pattern of elevated tTG antibodies by HLA risk subcategories consistent with previously established HLA-DQ risk gradients.³ However, the reference HLA risk groupings were generated in an at-risk population from the USA,³ and it has been shown that the prevalence of certain HLA alleles in individuals of different ethnocultural backgrounds with CD differs from the prevalence of such alleles in Caucasians with CD.⁴² Moreover, emerging evidence suggests that additional HLA variants may act as potential CD risk factors in certain ethnocultural groups, for example the HLA-DQ9.3 haplotype in individuals of Chinese descent.⁴³ This suggests that HLA risk stratification for CD may be population-dependent. Additionally, it is possible that other genetic regions that confer susceptibility to CD may be of increased importance in certain ethnocultural groups. Indeed, genome-wide studies have identified several other genetic variants that account for additional fractions of the genetic risk for CD.¹ It is possible that such variants, coupled with HLA-DQ genotypes, may be particularly useful in

establishing genetic risk gradients for CD in individuals of non-Caucasian ancestry.⁴² Nevertheless, a large screening study for CD in China found that all individuals with CD autoimmunity had the HLA-DQ2 genotype,²⁴ and further research is necessary to better understand the influence of ethnicity-specific genetic risk factors in the development of CD.

Many factors in addition to genetics are thought to contribute to risk of developing CD. Differences in per capita wheat consumption between countries are associated with the population prevalence of CD. Indeed, CD is rare in China and Japan, where per capita wheat consumption is relatively low and traditional diets are based on rice.^{5 18 26} The timing of first gluten exposure was long thought to play a role in the development of CD⁴⁴; however, this has recently been called into question and it is unclear whether the initial introduction of gluten into the diet influences risk of developing CD in at-risk infants.^{45 46} Exposure to certain viral infections during first introduction of gluten is thought to possibly prime the immune system and increase the risk of developing CD.^{47 48} Interactions between the gut microbiota and the intestinal mucosa can also affect the immune system.⁴⁹ Gut microbiota profiles have been shown to differ between patients with CD and healthy controls, and it is thought that bacteria-mediated inflammation in the mucosa may also play a role in the development of CD.⁵⁰ Dietary patterns are known to influence the composition of the gut microbiota.⁵¹ Furthermore, differences in dietary patterns between ethnicities have been identified.⁵² It is, therefore, possible that differences in broad dietary patterns between ethnocultural groups may explain some of the observed variation in the prevalence of CD between such groups.

CONCLUSION

We demonstrated that 1 in 114 Canadian adults (0.88%) has positive CD serology. We also report that 87% of cases are likely undiagnosed. Caucasians had the highest prevalence of positive CD serology as well as HLA-DQ2/8 elevated-risk alleles. While no individuals of East Asian or South Asian descent were found to have positive CD serology, high risk HLA-DQ2/8 alleles were equally prevalent in South Asians and Caucasians, but lower in East Asians. This study highlights the likely high prevalence of undiagnosed CD in Canada, and emphasises the importance of serological screening in patients with high-risk HLA genotypes.

Contributors JJ and AE-S designed the study. AE-S and DJAJ secured funding. JJ, CRV and SBD performed the analyses. JJ analysed the data and wrote the initial draft. All authors reviewed the manuscript. AE-S had primary responsibility for final content.

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Competing interests AE-S holds shares in Nutrigenomix, a genetic testing company for personalised nutrition. DJAJ has received research grants from

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Ethics approval Research Ethics Boards at the University of Toronto and St Michael's Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data will be made available to all interested researchers upon request to the corresponding author.

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