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Time trends, geographic variation and risk factors for gastroschisis in Canada: A population-based cohort study 2006–2017

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Abstract

Background: Previous studies showed increases in rates of gastroschisis in Canada in the first decade of the 21st century.

Objective: We sought to examine the epidemiologic characteristics of gastroschisis in Canada in recent years.

Methods: We conducted a retrospective population-based cohort study of all live-births and stillbirths delivered in Canada (excluding Quebec) from 2006 to 2017, with information obtained from the Canadian Institute for Health Information. Gastroschisis rates by maternal age, region of residence, and maternal and infant characteristics were quantified using prevalence rate ratios (RR) and 95% confidence intervals (CI). Log-binomial regression was used to quantify the associations between risk factors and gastroschisis.

Results: There were 1314 gastroschisis cases among 3 364 116 births. The prevalence rate was 3.7 per 10 000 total births in 2006 and 3.4 per 10 000 total births in 2017, with substantial annual variation in rates. The proportion of mothers aged 20–24 years decreased from 16.5% in 2006 to 11.3% in 2017, while the proportion of mothers aged <20 years halved from 4.8% to 2.3%. The prevalence of gastroschisis at birth remained unchanged among mothers aged <20, 20–24 and 30–49 years but increased among mothers aged 25–29 years. The age-adjusted prevalence rate of gastroschisis increased across the period (for 2016–2017 versus 2006–2007 rate ratio [RR] 1.28, 95% CI 1.05, 1.56), and there was substantial regional variation. Risk factors included problematic use of substances (RR 2.61, 95% CI 2.01, 3.39) and hypothyroidism (RR 2.76, 95% CI 1.56, 4.88). There was a North-to-South difference in gastroschisis prevalence (adjusted RR Far North compared with South 1.54, 95% CI 1.11, 2.15).

Conclusion: Gastroschisis birth prevalence rates in Canada have stabilised in recent years compared with the increase documented previously. The substantial geographic variation and North-to-South difference in gastroschisis prevalence may indicate variation in socio-economic status, lifestyle and nutritional patterns.

KEYWORDS
gastroschisis, lifestyle factors, socio-economic status, temporal trend

1 | BACKGROUND

Gastroschisis is a severe congenital malformation in which a portion of the intestine, and sometimes other abdominal organs, extrude through a defect in the abdominal wall, typically to the right of the umbilical cord. The birth prevalence of gastroschisis, once very rare, has increased worldwide since the 1960s, and it is still increasing in most regions.[1-3] However, both the reported rates and the time trends vary substantially by region and population subgroup, in part due to differences in ascertainment and registration by surveillance systems.[2,4,5] Geographic variation in the prevalence of gastroschisis and temporal increases have been observed worldwide.[6-9] In North Carolina (USA), a 130% increase was documented, with rates increasing from 2.0 in 1997 to 4.5 per 10 000 live births in 2000, primarily in offspring of mothers aged less than 20 years.[10] In Texas (USA), the overall prevalence of gastroschisis for the period 1999–2011 was 5.1 cases per 10 000 live births with a 4.8% annual increase.[3] The Canadian Congenital Anomalies Surveillance System (CCASS) reported an increase in the prevalence of gastroschisis from 3.1 per 10 000 total births in 2002 to 4.4 per 10 000 total births in 2009, with substantial regional variation.[11] The Canadian Pediatric Surgery Network (CAPSNet), using data from a national gastroschisis case-specific paediatric surgical database during the period of 2006–2011, found that younger maternal age, smoking, a history of pregestational or gestational diabetes, and medication to treat depression were associated with an increased risk of gastroschisis.[12] In addition to the well-established association with young maternal age, a recent systematic review reported positive associations with lifestyle factors such as maternal smoking, illicit drug use and alcohol consumption.[13] There is also a consistent inverse association of gastroschisis with maternal overweight and obesity.[13-15]

A North-to-South decreasing gradient in the prevalence rate of gastroschisis has been described in older data from Continental Europe, Great Britain, and Ireland but it is not clear whether this gradient has been stable, what factors account for it, and whether such a pattern exists in other regions.[2] In CAPSNet data for the period 2006–2011, there was significant spatial variation at the census division level in the birth prevalence of gastroschisis in Canada.[5] Some other studies also suggest small-area variations in the prevalence of gastroschisis at birth.[13,14,16] Additionally, reported rates of gastroschisis vary by ethnicity: studies from the USA have reported substantially higher rates of gastroschisis birth prevalence among non-Hispanic Whites compared with African Americans and Asians.[3,13,14]

This study aimed to examine recent temporal trends in gastroschisis birth prevalence in Canada from 2006 to 2017, to assess the association between known and potential maternal risk factors and gastroschisis prevalence at birth, and to quantify geographic variation and North-to-South gradient in gastroschisis prevalence at birth within Canada.

> **Synopsis**
>
> **Study question**
>
> - Has the increase in gastroschisis prevalence observed in Canada in the early 2000s continued, and what risk factors are associated with gastroschisis?
>
> **What's already known**
>
> - Gastroschisis rates have increased worldwide since the 1960s, but time trends vary geographically. Young maternal age is the most important risk factor.
>
> **What this study adds**
>
> - Between 2006 and 2017, the birth prevalence of gastroschisis in Canada did not show a clearly increasing or decreasing pattern. This stabilisation of the previously increasing gastroschisis rate is primarily attributable to the recent decline in births to women <25 years old.
> - There was substantial regional variation, including a North-to-South difference.
> - Lifestyle factors, including problematic use of substances, and, differences in maternal age distributions may account for the geographical variation.

2 | METHODS

2.1 | Study population and case ascertainment

This study included all livebirths and stillbirths (including late pregnancy terminations) registered in all hospitals in Canada (excluding Quebec) between 1 April 2006 and 31 March 2018. Data were obtained from the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD), which does not include information from hospitalisations in Quebec. The medical records of all mothers and babies at ≥20 weeks of gestation were examined: these records included information on gestational age, plurality, birthweight, maternal and newborn diagnoses (up to 25 diagnostic fields) and procedures (up to 20 intervention fields). During the study period, gastroschisis was typically detected prenatally with the diagnosis confirmed at birth, and this information was coded using

International Classification of Diseases codes (ICD-10CA Q793). The hospital discharge database has been checked for accuracy and previously used for public health and perinatal research and surveillance.[17-19]

2.1.1 | Mother-newborn dyads and covariates

Live-born infants were linked to their mothers through a CIHI-assigned maternal-newborn number assigned at birth, and stillbirths (including foetuses from late pregnancy terminations) were linked to their mothers through a previously validated linkage algorithm, with deterministic and/or probabilistic components.[19] Informed by previous studies,[12,13] maternal characteristics and other risk factors studied included age, multiple pregnancy, parity, pre-gestational or gestational diabetes, infant sex, maternal chronic conditions or illnesses (including lupus, epilepsy or migraine diagnoses or non-chromosomal congenital abnormalities), obesity, problematic tobacco use, problematic use of substances (ie alcohol, opioid, cannabinoids, cocaine, other specified/unspecified drugs or mothers delivering an infant with neonatal abstinence syndrome)[20] and use of medication to treat depression. Because of reported increases in detection of thyroid conditions in young women in a number of jurisdictions, likely due to increasing diagnostic scrutiny, preliminary analyses also examined thyroid disorders, and subsequent analyses focussed on hypothyroidism. Details on definitions and coding are included in Table S1. Rural or urban maternal residence was identified using the forward sortation area of the residential postal code.[21] Maternal geographic location (eg northern British Columbia, northern Alberta or northern Manitoba) and latitude were defined using the first 3 digit of the residential postal code and according to North-to-South transition lines.[22]

2.1.2 | Region or sub-region & and North-to-South gradient categorisation

All data on live births and stillbirths occurring in the study period were stratified into the following 21 sub-regions based on 3-digit postal codes of maternal residence: the Northwest Territories, the Yukon and Nunavut (3 sub-regions); northern and southern British Columbia, Alberta, Saskatchewan and Manitoba (8 sub-regions); northern, central, western, eastern Ontario or metropolitan Toronto (5 sub-regions); Quebec (1 sub-region, solely for residents who gave birth at hospitals in other provinces); and New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland and Labrador (4 sub-regions). We also created a surrogate variable to represent the North-to-South difference in Canadian geography[23]: Far North consisting of the three Territories; North consisting of British Columbia, Alberta, Saskatchewan, Manitoba, northern Ontario, northern Quebec and Labrador; South consisting of western, central and eastern Ontario, metropolitan Toronto, New Brunswick, Nova Scotia, and Prince Edward Island, Newfoundland and southern Quebec.

2.1.3 | Statistical analysis

We examined temporal trends in the prevalence rate of gastroschisis. We first evaluated non-linear trends in prevalence rates by including the linear and non-linear component based on cubic spline terms.[24] Maternal age was initially modelled using indicator variables (for categories <20, 20–24, 25–29 and 30–49 years, with 25–29 years as the reference age group) and then modelled using a quadratic term for age given the non-linear relation with gastroschisis. For ease of interpretation, the maternal age-gastroschisis relation was also modelled using finer age categories (ie 14–17; 2-year age categories: 18–19, 20–21, 22–23 (reference), 24–25; 3-year categories: 26–28, 29–31, 32–34; 35–49 years as a single category). We included maternal residence (rural versus urban) to potentially account for variations in accessibility to prenatal screening/diagnosis and subsequent termination, and because this variable is a partial surrogate for socio-economic status (SES).[25]

A log-binomial regression model with a Poisson distribution was used to model univariate and multivariable associations. Both univariate and multivariable rate ratios with 95% confidence intervals were estimated, with the latter adjusting for maternal characteristics, including maternal age and other covariates. Analyses of regional variation and a potential North-to-South gradient in gastroschisis prevalence included crude comparisons and a comparison adjusted for maternal age and other potential confounders.

Analyses were also conducted to examine issues related to the robustness of the results to unmeasured confounding using E-value methodology.[26] The E-value is a measure related to evidence for causality and represents the minimum strength of association that an unmeasured confounder would need to have with both a foetal exposure and gastroschisis birth, conditional on the confounders in the regression model, to fully explain the observed association.[26]

2.2 | Missing data

The data used in this study were abstracted from childbirth hospitalisation records. Data on obesity, which is inconsistently documented in medical records as a medical diagnosis, were underestimated. Data on parity were not reported by certain provinces/territories; and therefore, there is systematic missingness for this variable.[27] We treated the missing values for parity as a specific category in the analysis rather than imputing data.

2.3 | Ethics approval

The study was carried out under the surveillance mandate of the Public Health Agency of Canada (with privacy safeguards), and ethics approval was not required.

3 | RESULTS

There was a total of 1314 gastroschisis cases (1226 or 93.3% among live births and 55 or 4.2% among stillbirths and 33 or 2.5% among late terminations) among 3,364,116 hospital births in Canada (excluding Quebec) between 2006 and 2017, with an overall birth prevalence of 3.9 per 10 000 total births. There was no non-linear relationship between year and gastroschisis rate. Linear time trend analysis showed an overall non-significant decrease ($P = 0.053$); the annual prevalence rate increased from 3.7 (95% CI 3.0, 4.5) in 2006 to 5.0 (95% CI 4.2, 5.9) in 2009 and declined to 3.4 (95% CI 2.8, 4.2) per 10 000 total births in 2017 (Figure 1). The proportion of Canadian mothers aged 20–24 years decreased from 16.6% in 2006 to 11.3% in 2017, and the proportion of mothers <20 years halved from 4.8% to 2.3%, while the proportion of mothers ≥30 years increased from 49.4% in 2006 to 59.1% in 2017 (Figure S1).

There were no temporal changes in gastroschisis birth prevalence rates among women aged <20, 20–24 and 30–49 years, although rates increased among women aged 25–29 years (Figure 2). Age-adjustment altered the overall gastroschisis temporal trend and showed a 28% (95% CI 5%, 56%) increase in age-adjusted gastroschisis prevalence in 2016–2017 compared with 2006–2007 (indicating a substantial role played by declines in the proportion of young women over the study period; Table 1).

Prevalence rates declined markedly with advancing maternal age: gastroschisis birth prevalence rates were highest among younger women, with rates of 26.3, 27.0 and 15.6 per 10 000 total births among mothers aged 14–17, 18–19 and 20–21 years, respectively, and much lower rates among older women (eg 0.5 per 10 000 total births among women 35–49 years). Higher rates of gastroschisis were observed in nulliparous mothers, mothers with rural residence, those reported to have problematic use of tobacco or problematic use of substances, mothers with chronic illness and mothers with a depressive episode or recurrent depressive disorder. Lower gastroschisis rates were observed among women with gestational diabetes mellitus (Table 2). Multivariable adjustment did not alter the significant positive associations between gastroschisis and younger maternal age, higher parity and rural residence. Other noteworthy associations included an inverse association with gestational diabetes, and positive associations with mothers reported to have problematic use of substances and mothers with hypothyroidism (Table 2).

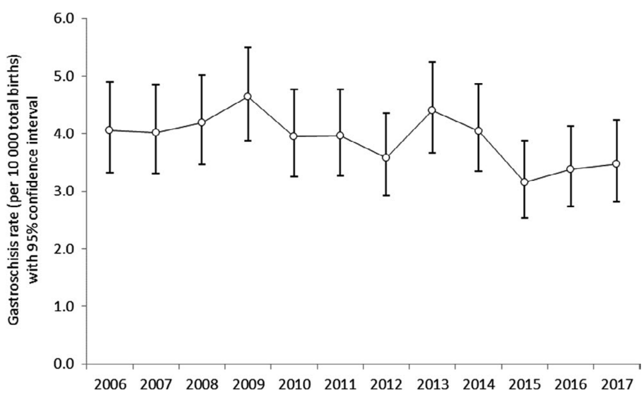

FIGURE 1 Annual birth prevalence rates (and 95% Confidence Interval) of gastroschisis among total births in Canada (excluding Quebec), 2006 and 2017

FIGURE 2 Annual gastroschisis birth prevalence rates by maternal age, Canada (excluding Quebec), 2006–2017

Table 3 shows that the highest prevalence of gastroschisis was observed in Nunavut (17.2 per 10 000 total births, 95% CI 11.2, 25.2), northern Manitoba (15.4 per 10 000 total births, 95% CI 9.7, 23.0) and northern Saskatchewan (10.4 per 10 000 total births, 95% CI 6.7, 15.5), contrasted with a reference rate of 3.7 per 10 000 total births (95% CI 3.1, 4.4) in southwestern Ontario. Low rates of gastroschisis were observed in metropolitan Toronto and central Ontario. After adjusting for maternal characteristics (including age, parity and rural residence) and other covariates, the sub-regional variation diminished substantially: only Northern and Southern Manitoba, southern Saskatchewan, Quebec and Nunavut showed significant higher prevalence rate ratios compared with Southwestern Ontario (Table 3).

Table 4 shows a decrease in the prevalence of gastroschisis from North to South. The highest rates of gastroschisis were observed for women in the Far North (9.9 per 10 000 total births), followed by the North (4.9 per 10 000 total births), while the lowest rate was seen in the South (3.1 per 10 000 total births). Adjusting for maternal characteristics and other covariates attenuated this variation, with the birth prevalence of gastroschisis 1.5-fold higher in the Far North and 1.3-fold higher in the North as compared with the South.

Stratified analyses of the association between gastroschisis and problematic use of substances (rate ratio [RR] 2.61, 95% confidence interval [CI] 2.01, 3.39) showed that maternal use of cannabinoids (RR 2.87, 95% CI 1.85, 4.44), opioids (RR 1.77, 95% CI 1.12, 2.82) and miscellaneous substances (RR 1.87, 95% CI 1.04, 3.36) were positively associated with increased risk of gastroschisis (Table S2).

E-values for associations between gastroschisis and maternal risk factors are included in Table S3. E-values for the association between hypothyroidism ($E = 4.96$) and problematic use of substances among pregnant women ($E = 4.66$) suggested that relatively strong confounding assumptions would be needed to eliminate the association between these factors and the risk of gastroschisis.

TABLE 1 Time trends in gastroschisis prevalence and rate ratio, Canada (excluding Quebec), 2006–2007 to 2016–2017

Year of infant birth	Number of mother-newborn dyads	Cases	Per 10 000	Unadjusted rate ratio (95% confidence interval)	Maternal age-adjusted rate ratio[a] (95% confidence interval)
2006–2007	537 095	194	3.6	1.00 (Reference)	1.00 (Reference)
2008–2009	565 942	268	4.7	1.31 (1.09, 1.58)	1.33 (0.71, 1.60)
2010–2011	562 784	231	4.1	1.14 (0.94, 1.38)	1.22 (0.78, 1.33)
2012–2013	563 525	223	4.0	1.09 (0.90, 1.33)	1.26 (0.92, 1.48)
2014–2015	568 910	205	3.6	0.99 (0.82, 1.21)	1.24 (1.04, 1.49)
2016–2017	565 860	193	3.4	0.94 (0.77, 1.15)	1.28 (1.05, 1.56)
Total	3 364 116	1314	3.9		

[a]Adjusted for maternal age (<20, 20–24, 25–29 and 30–49 years).

TABLE 2 Association between characteristics of mother-newborn dyads and gastroschisis, Canada (excluding Quebec), 2006–2017

		Cases ($n = 1314$)	Rate ratio (95% confidence interval)		
Characteristic	Number of deliveries (%)	Number (rate per 10 000)	Unadjusted	Adjusted[a]	Adjusted[b]
Maternal age at conception (year)					
Maternal age (year)					
14–17	38 821 (1.2)	102 (26.3)	2.74 (2.15, 3.48)	2.43 (1.90, 3.09)	
18–19	88 556 (2.6)	239 (27.0)	2.81 (2.33, 3.40)	2.61 (2.15, 3.16)	
20–21	148 291 (4.4)	231(15.6)	1.62 (1.34, 1.96)	1.57 (1.30, 1.90)	
22–23	203 048 (6.0)	195 (9.6)	1.00 (Reference)	1.00 (Reference)	
24–25	276 876 (8.2)	159 (5.7)	0.60 (0.48, 0.74)	0.61 (0.49, 0.75)	
26–28	587 234 (17.5)	186 (3.2)	0.33 (0.27, 0.40)	0.34 (0.28, 0.42)	
29–31	719 599 (21.4)	114 (1.6)	0.16 (0.13, 0.21)	0.18 (0.14, 0.22)	
32–34	630 033 (18.7)	54 (0.9)	0.09 (0.07, 0.12)	0.10 (0.07, 0.13)	
35–49	671 658 (20.0)	34 (0.5)	0.05 (0.04, 0.08)	0.06 (0.04, 0.09)	
Multiple pregnancy					
Yes	58 257 (1.7)	12 (2.1)	0.62 (0.35, 1.09)	0.93 (0.53, 1.64)	0.93 (0.53, 1.65)
No	3 305 859 (98.3)	1302 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Parity					
1st child	1 168 648 (34.7)	658 (5.6)	2.71 (2.31, 3.18)	1.59 (1.35, 1.88)	1.56 (1.32, 1.84)
2nd child	918 721 (27.3)	191 (2.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
≥3rd child	578 983 (17.3)	133 (2.3)	1.11 (0.89, 1.38)	1.46 (1.17, 1.83)	1.45 (1.05, 1.81)
Missing data	697 764 (20.7)	332 (4.8)	2.28 (1.91, 2.73)	1.92 (1.60, 2.29)	1.90 (1.58, 2.27)
Rural residence					
Yes	568 492 (16.9)	364 (6.4)	1.88 (1.67, 2.13)	1.24 (1.09, 1.40)	1.23 (1.08, 1.39)
No	2 795 624 (83.1)	950 (3.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Newborn sex					
Male	1 725 821 (51.6)	678 (3.9)	1.01 (0.91, 1.13)	1.01 (0.91, 1.13)	1.01 (0.91, 1.13)
Female	1 638 295 (48.4)	636 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Prepregnancy diabetes					
Yes	26 138 (0.3)	<5 (1.5)	0.39 (0.15, 1.04)	0.43 (0.28, 1.45)	0.55 (0.21, 1.47)
No	337 978 (99.7)	1310 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Gestational diabetes					

(Continues)

TABLE 2 (Continued)

Characteristic	Number of deliveries (%)	Cases (n = 1314) Number (rate per 10 000)	Rate ratio (95% confidence interval) Unadjusted	Adjusted[a]	Adjusted[b]
Yes	210 395 (6.3)	20 (1.0)	0.23 (0.15, 0.36)	0.43 (0.28, 0.67)	0.44 (0.28, 0.68)
No	3 153 721 (93.7)	1294 (4.2)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Chronic illness[c]					
Yes	32 559 (1.0)	20 (6.1)	1.58 (1.02, 2.46)	0.91 (0.47, 1.76)	0.93 (0.48, 1.78)
No	3 331 557 (98.6)	1294 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Obesity					
Yes	52 973 (1.6)	12 (2.3)	0.58 (0.33, 1.02)	0.55 (0.36, 1.36)	0.65 (0.37, 1.15)
No	3 311 143 (98.4)	1302 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Problematic tobacco use					
Yes	20 135 (0.6)	23 (11.4)	2.96 (1.96, 4.47)	1.23 (0.81, 1.88)	1.25 (0.82, 1.89)
No	343 981 (99.4)	1291 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Problematic use of substances[d]					
Yes	33 963 (1.0)	62 (18.3)	4.86 (3.76, 6.26)	2.59 (1.99, 3.36)	2.61 (2.01, 3.39)
No	3 330 153 (99.0)	1302 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Depressive disorders					
Yes	10 713 (0.3)	11 (10.2)	2.64 (1.46, 4.78)	2.27 (0.94, 5.48)	2.25 (0.93, 5.43)
No	3 353 402 (99.7)	1303 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Hypothyroidism					
Yes	24 383 (0.7)	12 (4.9)	1.26 (0.72, 2.23)	2.72 (1.54, 4.82)	2.76 (1.56, 4.88)
No	3 336 055 (99.3)	1302 (3.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Overall	3 364 116 (100)	1314 (3.9)			

[a]Adjusted for all variables in the table, with maternal age modelled using indicator variables.

[b]Adjusted for all variables in the table, with maternal age modelled using a quadratic term.

[c]Including lupus, epilepsy, migraine or non-chromosomal anomaly among mothers.

[d]Problematic use of alcohol, opioids, cocaine or cannabinoids or other specified or unspecified (miscellaneous) drugs or mothers delivering an infant with neonatal abstinence syndrome (NAS).[20]

4 | COMMENT

4.1 | Principal findings

In this population-based study in Canada, a country with vast geography, we observed an essentially unchanged birth prevalence of gastroschisis during the period of 2006–2017. Annual rates of gastroschisis birth prevalence had relatively wide confidence intervals and rates fluctuated between 2006 and 2017 without any clear increasing or decreasing pattern. This essentially stable pattern is encouraging as gastroschisis rates were reported to have been increasing in Canada in previous years.[11] Younger maternal age, a strong risk factor which decreased in frequency, acted to reduce the birth prevalence of gastroschisis, while changes in risk factors such as problematic use of substances, hypothyroidism and other risk factors may have contributed to increasing the frequency of gastroschisis. We also observed substantial regional variation, which appeared to be at least partly attributable to differences in maternal age, rural residence and other maternal factors such as the rate of gestational diabetes. Furthermore, we observed a decrease in gastroschisis prevalence from North to South within Canada, although this decreasing gradient was attenuated substantially after adjustment for maternal age and other factors.

4.2 | Strengths of the study

We carried out a large, population-based study, which used 12 years of data from a validated data source. Information on maternal conditions (such as diabetes mellitus) and residence (ie rural vs urban, or northern regions or territories) was accurately captured in our data source.[21] This database has been validated and previously used for public health and perinatal epidemiologic research and surveillance.[17,18] Extensive checks are made on data that flow into

TABLE 3 Numbers and rates of gastroschisis among total births in Canada, according to province/territory or sub-region of residence, 2006–2017

Geographic region	Total births	Number	Rate (95% CI)[a]	Unadjusted rate ratio (95% CI)	Adjusted rate ratio[b] (95% CI)
Newfoundland and Labrador	52 458	28	5.3 (3.5, 7.7)	1.44 (0.95, 2.18)	1.31 (0.86, 1.97)
Prince Edward Island	14 840	9	6.1 (2.8, 1.5)	1.64 (0.83, 3.22)	1.53 (0.78, 3.01)
Nova Scotia	100 490	52	5.2 (3.9, 6.8)	1.40 (1.01, 1.94)	1.27 (0.91, 1.76)
New Brunswick	81 324	44	5.4 (3.9, 6.8)	1.46 (1.03, 2.07)	1.17 (0.83, 1.66)
Quebec[c]	22 409	15	6.7 (3.7, 11.0)	1.81 (1.05, 3.09)	2.38 (1.39, 4.07)
Eastern Ontario	226 802	72	3.2 (2.5, 4.0)	0.86 (0.64, 1.15)	0.95 (0.71, 1.78)
Central Ontario	619 404	132	2.1 (1.8, 2.5)	0.57 (0.45, 0.74)	0.84 (0.66, 1.08)
Northern Ontario	90 933	63	6.9 (5.3, 8.9)	1.87 (1.37, 2.54)	1.30 (0.96, 1.78)
Southwestern Ontario	310 261	115	3.7 (3.1, 4.4)	1.00 (Reference)	1.00 (Reference)
Metropolitan Toronto	351 228	57	1.6 (1.2, 2.1)	0.44 (0.32, 0.60)	0.70 (0.51, 0.96)
Northern Manitoba	14 979	23	15.4 (9.7, 23.0)	4.14 (2.65, 6.48)	1.87 (1.18, 2.91)
Southern Manitoba	170 520	112	6.6 (5.4, 7.9)	1.77 (1.37, 2.30)	1.55 (1.19, 2.01)
Northern Saskatchewan	23 088	24	10.4 (6.7, 15.5)	2.80 (1.81, 4.35)	1.34 (0.86, 2.08)
Southern Saskatchewan	145 781	99	6.8 (5.5, 8.3)	1.83 (1.40, 2.40)	1.50 (1.15, 1.97)
Northern Alberta	27 029	16	5.9 (3.4, 9.6)	1.60 (0.95, 2.69)	0.95 (0.56, 1.61)
Southern Alberta	574 217	213	3.7 (3.2, 4.2)	1.00 (0.80, 1.26)	1.07 (0.86, 1.35)
Northern British Columbia	22 652	7	3.1 (1.2, 6.4)	0.83 (0.33, 1.79)	0.68 (0.31, 1.45)
Southern British Columbia	475 169	193	4.1 (3.5, 4.7)	1.10 (0.87, 1.38)	1.45 (1.15, 1.83)
Northwest Territories	16 242	8	4.9 (2.1, 9.7)	1.33 (0.65, 2.72)	0.94 (0.46, 1.92)
Nunavut	15 132	26	17.2 (11.2, 25.2)	4.64 (3.03, 7.09)	1.95 (1.27, 2.99)
Yukon	9158	6	6.6 (2.4, 14.3)	1.77 (0.78, 4.02)	1.79 (0.79, 4.08)
Canada	3 364 116	1314	3.9 (3.7, 4.1)	–	–

[a]Per 10 000 total births; CI = confidence interval.

[b]Adjusted for maternal age (age and age^2 in years), prepregnancy diabetes, gestational diabetes, chronic illness, obesity, problematic use of tobacco, problematic use of substances, depressive disorders and hypothyroidism.

[c]Based on postal codes of maternal residence and refers to Quebec residents who gave birth at hospitals in other provinces.

TABLE 4 North-to-south difference in prevalence rate ratio (RR) of gastroschisis in Canada

Latitude of residence[a]	Total births	Cases	Rate per 10 000 total births	Unadjusted RR (95% CI)	Adjusted RR[b] (95% CI)
Far North	40 532	40	9.9	3.19 (2.31, 4.39)	1.54 (1.11, 2.15)
North	1 385 749	674	4.9	1.57 (1.41, 1.75)	1.29 (1.15, 1.45)
South	1 937 835	600	3.1	1.00 (Reference)	1.00 (Reference)
Total	3 364 116	1314	3.9		

[a]North-to-south difference as defined in methods.

[b]Adjusted for maternal age (age and age^2 in years), multiple pregnancy, parity, rural residence, newborn sex, prepregnancy diabetes, gestational diabetes, chronic illness, obesity, problematic use of tobacco, problematic use of substances, depressive disorders and hypothyroidism.

Discharge Abstract Database before it is released.[27] In addition, the diverse sub-regions and vast geography of Canadian territories permit examination of a North-to-South difference.

4.3 | Limitations of the data

Our study also has a few limitations. Covariates such as obesity were severely under-reported, and diagnostic codes only documented problematic use of tobacco and substances (and not any recreational tobacco and substance use). Thus, the lack of association between problematic tobacco use (frequency 0.6%) and gastroschisis in our study does not imply a lack of association between any tobacco use and gastroschisis. We could not rule out the possibility that some pregnancies with gastroschisis were medically terminated prior to 20 weeks' gestation. However, termination of pregnancy for gastroschisis is uncommon as shown in previous work in Canada: prognosis is good with surgical correction after birth and few gastroschisis cases are associated with other malformations or genetic disorders.[28] In addition, early ultrasound screening of congenital anomalies is typically directed at identifying neural tube defects and critical heart defects.[19,29,30] Although obesity and substance use have important implications for maternal, foetal and infant health, the recording of such information is not consistent in medical charts and analysis based on the coded data in the national hospitalisation database seriously underestimates the prevalence of obesity. The ICD-10 codes for obesity and problematic substance use identified an overall frequency of 1.6% and 1.7%, respectively, in the Discharge Abstract Database.[19,31] Approximately 20% of the population had missing values for parity; women with missing information had a risk of gastroschisis that was similar to the average risk for nulliparous and parous women (Table 2). Furthermore, our sensitivity analysis assessing the strength of the association (of an unmeasured confounder) required to nullify our findings showed that our results are likely robust.[26] Better understanding of maternal prenatal exposures that increase the risk of gastroschisis will depend on large studies with prospectively collected prenatal information.[32]

4.4 | Interpretation

Our findings are generally consistent with previous studies,[12-14] indicating that the prevalence of gastroschisis is associated with several lifestyle risk factors including use of substances. While the exact cause of gastroschisis remains unknown, this malformation is believed to have a multifactorial aetiology.[2,14,33] Gastroschisis occurs more frequently among young mothers and among mothers who smoke tobacco during pregnancy, drink alcohol, use recreational drugs and mothers from a lower socio-economic status.[13,33-40] Several reports have shown that gastroschisis is associated with maternal vasoconstrictive medication use,[36] and bronchodilator use during pregnancy.[39] It has also been suggested recently that gastroschisis is associated with cumulative maternal stressor exposures.[40]

In our study, younger maternal age was a strong risk factor for gastroschisis. Rural residence, parity, problematic use of substances and hypothyroidism were also associated with gastroschisis. These risk factors were confounders in our study and multivariable adjustment attenuated or abolished associations between chronic disease, problematic tobacco use and depressive disorders and gastroschisis. Younger maternal age likely confounded the association between tobacco use and gastroschisis, while problematic substance use may have confounded the association between chronic disease and gastroschisis. The association with hypothyroidism does not appear to have been previously reported, although an association between gastroschisis and anti-depressant medication has been shown previously.[12] In addition, we found a positive association between maternal rural residence and gastroschisis. This association was no longer significant after adjustment for sub-region of residence (rate ratio 1.08, 95% CI 0.94, 1.24), and this was likely because of collinearity between the sub-region of residence and rural residence (large urban centres are mostly located in southern settings).

Our study showed a 2.6-fold higher risk of gastroschisis associated with overall problematic use of substances (Table 2) and a 2.9-fold and a 1.8-fold higher risk of gastroschisis with cannabinoids and opioids, respectively (Table S2). We posit that the increasing maternal age-adjusted temporal trend in gastroschisis (Table 1) may be partly due to changes in such lifestyle factors among young women, although study limitations prevent us from making a definitive conclusion. Our study lacked data obtained routinely on tobacco, substance and medication use from all mothers, and therefore, we could only examine associations between administrative data collected on problematic tobacco use, and problematic use of substances, and gastroschisis. Recent Canadian surveys on tobacco, alcohol and drugs have reported that the prevalence of past-year use of illegal drugs including cannabis was 15%, and the past-year problematic use of illegal drugs was higher among youth aged 15–19 years (20%) and young adults aged 20–24 years (35%) compared with adults aged 25 years and older (13%).[41]

The recent US National Birth Defects Prevention Study identified an inverse association between gestational diabetes and gastroschisis (odds ratio 0.5, 95% CI 0.3, 0.8)[42] that was similar in magnitude to the association documented in our study (rate ratio 0.44, 95% CI 0.28, 0.68, Table 2). Unmeasured lifestyle factors such as nutritional status and prepregnancy BMI may at least partially explain this association between gestational diabetes and gastroschisis. On the other hand, studies that have examined a history of diabetes (type 1, type 2 and gestational) have shown diabetes to be a risk factor for gastroschisis.[12]

The change in temporal and other associations following adjustment for maternal age and other risk factors needs to be interpreted with care. The crude temporal trend showed no systematic change in gastroschisis birth prevalence between 2006 and 2017, while the age-adjusted pattern showed a rising trend. This implies that reductions in births to younger mothers (the highest risk group for gastroschisis) acted to prevent a rise in gastroschisis prevalence. Similarly, the significant attenuation of the high rate ratios associated with residence in the far north and northern regions following adjustment for maternal age and other risk factors (eg rural residence and problematic substance use) suggests that these factors explain a substantial portion, but not all, of the higher risk for gastroschisis seen in these regions. It is possible that the North-to-South difference that persists after adjusting for maternal characteristics, and covariates are due to unmeasured variation in socioeconomic status, lifestyle and nutritional patterns.[13,22-24,43,44]

5 | CONCLUSIONS

Previous studies have shown increases in rates of gastroschisis in Canada in the first decade of the 21st century. However, fewer births to younger mothers appear to have resulted in a stabilisation of gastroschisis prevalence rates in Canada between 2006 and 2017. Our findings on prenatal determinants and risk factors for gastroschisis indicate that both maternal biologic immaturity and unfavourable *in utero* exposures (eg lifestyle factors, problematic substance use and nutritional patterns that are probably associated with rural and northern residence) play a role in the occurrence of gastroschisis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Canadian Institute for Health Information (CIHI). Data sharing agreements prohibit PHAC from making the dataset publicly available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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