Spatial variability of gastroschisis in Canada, 2006–2011: An exploratory analysis

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ABSTRACT

OBJECTIVES: Gastroschisis is a serious birth defect of the abdominal wall that is associated with mortality and significant morbidity. Our understanding of the factors causing this defect is limited. The objective of this paper is to describe the geographic variation in incidence of gastroschisis and characterize the spatial pattern of all gastroschisis cases in Canada between 2006 and 2011. Specifically, we aimed to ascertain the differences in spatial patterns between geographic regions and identify significant clusters and their location.

METHODS: The study population included 641 gastroschisis cases from the Canadian Pediatric Surgery Network (CAPSNet) database, a population-based dataset of all gastroschisis cases in Canada. Cases were geocoded based on maternal residence. Using Statistics Canada live-birth data as a denominator, the total prevalence of gastroschisis was calculated at the provincial/territorial levels. Random effects logistic models were used to estimate the rates of gastroschisis in each census division. These rates were then mapped using ArcGIS. Cluster detection was performed using Local Indicators of Spatial Association (LISA).

RESULTS: There is significant spatial heterogeneity of the rate of gastroschisis across Canada at both the provincial/territorial and census-division level. The Yukon, Northwest Territories and Prince Edward Island have higher overall rates of gastroschisis relative to other provinces/territories. Several census divisions in Alberta, Manitoba, Saskatchewan, Ontario, Northwest Territories and British Columbia demonstrated case "clusters", i.e., focally higher rates in discrete areas relative to surrounding areas.

CONCLUSIONS: There is clear evidence of spatial variation in the rates of gastroschisis across Canada. Future research should explore the role of area-based variables in these patterns to improve our understanding of the etiology of gastroschisis.

KEY WORDS: Spatial analysis; gastroschisis; cluster analysis; Canada

La traduction du résumé se trouve à la fin de l'article.

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Gastroschisis is a serious congenital abdominal wall defect in which the intestines extrude through a paraumbilical defect into the amniotic cavity. Infants born with this condition are more likely to be born preterm and to have had poor fetal growth.[1] This anomaly requires immediate postnatal surgery, which has a good outcome, with most contemporary series reporting survival rates of over 90%.[2] Infants who have had the surgery require a resource-intensive, neonatal intensive care unit stay averaging 6 weeks.[3] A subset of infants with gastroschisis who suffer a more severe form of intestinal injury require prolonged hospitalization, specialized nutrition, multiple surgeries and in some instances organ transplantation to survive.[4]

One of the most interesting and concerning aspects of gastroschisis is the well-documented increasing global prevalence. Data from the Public Health Agency of Canada indicates that the rate of gastroschisis has increased from 1 per 3,300 in 2003 to 1 per 2,200 live births in 2009.[5] This parallels reports from the US and Europe.[6,7] The causes of gastroschisis are largely unknown, although it is believed to be of multifactorial etiology and primarily non-genetic. The most consistently observed risk factor that has been identified is young maternal age, in particular <20 years of age.[8] It has been suggested that women aged 14 to 19 years are seven times more likely to have an infant with gastroschisis compared with women aged 25 to 29 years.[9] However, it is not certain what the mechanism is by which maternal age influences the development of gastroschisis in the fetus. One possible explanation is the potential relationship between teratogenic exposures and risk behaviours, including smoking, use of recreational drugs, poor nutrition and increased rates of infection that may be more common in younger mothers. In addition to maternal age, several other risk factors have been suggested, including young paternal age,[10] low socio-economic status (SES) and deprivation,[11,12] smoking,[13] alcohol and illicit drug

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use during pregnancy,[14] maternal medications,[15] infection,[16] and environmental factors like exposure to pesticides.[17]

There is evidence that suggests considerable geographic variation in the occurrence of gastroschisis. For example, geographic gradients of decreasing prevalence from North to South have been suggested in Continental Europe and Britain.[18,19] A study from North Carolina has demonstrated spatial clustering of gastroschisis cases after controlling for other risk factors,[20] and a health impact comparison of SES-matched residents living near or remote from a landfill in South Wales demonstrated gastroschisis case clustering near the landfill.[21] This has not yet been examined in Canada. Understanding the geographic distribution of gastroschisis can be useful, particularly given its unknown etiology. Identification of disease clusters may assist in the development of novel hypotheses about the area-level factors that may predispose to a pregnancy complicated by gastroschisis. Using a disease-specific national dataset, we aimed to describe the spatial pattern of all cases of gastroschisis in Canada between 2006 and 2011 and specifically, to ascertain how gastroschisis clusters within different geographic regions.

METHODS

We conducted a cross-sectional, population-based, ecological-level analysis to assess the spatial pattern of gastroschisis in Canada. Study data were obtained from the Canadian Pediatric Surgery Network (CAPSNet) database, which represents 16 Canadian pediatric hospitals, each with an on-site or functionally linked high-risk obstetrical centre, a level III neonatal intensive care unit, and availability of pediatric subspecialty surgery and anesthesia. CAPSNet is among the largest and most comprehensive compilation of anonymized, patient-level, population-based data for gastroschisis available in the world, and is set up to capture all cases of gastroschisis in Canada.

The study population included gastroschisis cases diagnosed between January 2006 and December 2011. Cases were ascertained at prenatal diagnosis (if one was made) or after birth, and data were abstracted from diagnosis to death or discharge. Pregnancies resulting in stillbirths or terminations were included. Details related to data abstraction, de-identification, centralization, and privacy protection during data handling have been described previously.[3] Ethics approval for this study was received from the UBC Children's and Women's Research Ethics Board. In addition, data collection at the individual centres was authorized by each centre's research ethics board.

For each gastroschisis case, maternal postal codes were used to identify the home address. When patients were transferred out of province or the territories to access pre- or postnatal health services, the postal code used was that of their home residence. This was used to geocode all cases using Postal Code Conversion File Plus (PCCF+), a validated geocoding program available through Statistics Canada. The cases that could not be geocoded ($n = 31$) were excluded from the analysis. A comparison was made between these 31 cases and the rest of the study population for characteristics, including maternal age, proportion of stillbirths, ethnicity, gestational age and gender, and no statistically significant differences were found between the two groups.

Statistics Canada data on live births at the provincial and census division levels were used to calculate the total prevalence of gastroschisis, by using the rates of new gastroschisis cases (including live births, stillbirths and terminations) as the numerator and total live births over the same time period as the denominator. Age-standardized rates were also calculated using direct standardization. The population of all mothers with live births in 2009 was used as the standard population (Statistics Canada, Canadian Vital Statistics, Birth Database (CANSIM table 102–4503)). The 95% confidence intervals for crude and age-standardized rates were calculated using the methods described in Fleiss et al.[22] Random effects logistic models were used to estimate the rates of gastroschisis in each census division. This approach was used to smooth the rates and accommodate for the variability resulting from the majority of cells having low counts. The geospatial software, ArcGIS version 10, was used to create descriptive maps of gastroschisis rates as a proportion of all live births during the same time period (Environmental Systems Research Institute, Redlands, CA). Descriptive statistical analysis was conducted using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

To identify spatial autocorrelation, the Local Indicator of Spatial Association (LISA) was applied. The LISA measures whether for each census division the rate of gastroschisis is closer to the values of its neighbours or to the national average. Rejection of the null hypothesis implies a nonrandom spatial pattern referred to as spatial autocorrelation. The Moran's I statistic is a global measure of spatial autocorrelation and was used as a measure of the overall clustering. Moran's I ranges in value from +1 (for positive spatial autocorrelation) to −1 (negative autocorrelation). Positive spatial autocorrelation implies that similar rates of gastroschisis pregnancies are clustered geographically (tend to occur in adjacent census divisions), while negative autocorrelation indicates a geographically dispersed spatial trend. To test for statistical significance, the LISA analysis used local Moran's I indicator at the 0.05 significance level using a Monte Carlo permutation approach.

Table 1. Rate of gastroschisis by province/territory, 2006–2011

Province/territory	Rate per 100,000 live births (95% CI)	Age-standardized rate* (95% CI)
Alberta	27 (21–34)	24 (19–31)
British Columbia	35 (28–43)	37 (30–45)
Manitoba	40 (28–55)	29 (19–41)
New Brunswick	46 (28–71)	34 (19–54)
Newfoundland and Labrador	56 (32–91)	51 (29–82)
Nova Scotia	45 (29–67)	40 (26–60)
Ontario	26 (23–30)	26 (22–29)
Prince Edward Island	82 (33–169)	68 (26–137)
Quebec	23 (19–27)	22 (19–27)
Saskatchewan	23 (14–36)	15 (8–25)
Yukon	90 (11–325)	89 (11–325)
Northwest Territories	118 (38–274)	68 (15–170)
Nunavut	123 (45–268)	36 (5–115)

* There were 42 infants with missing maternal age information that were not included in the age-standardized rate.

RESULTS

A total of 641 cases of gastroschisis were identified. Table 1 illustrates a calculated prevalence of gastroschisis by province and territory. The prevalence rate for gastroschisis in Canada ranges between 23 per 100,000 in Quebec and Saskatchewan to

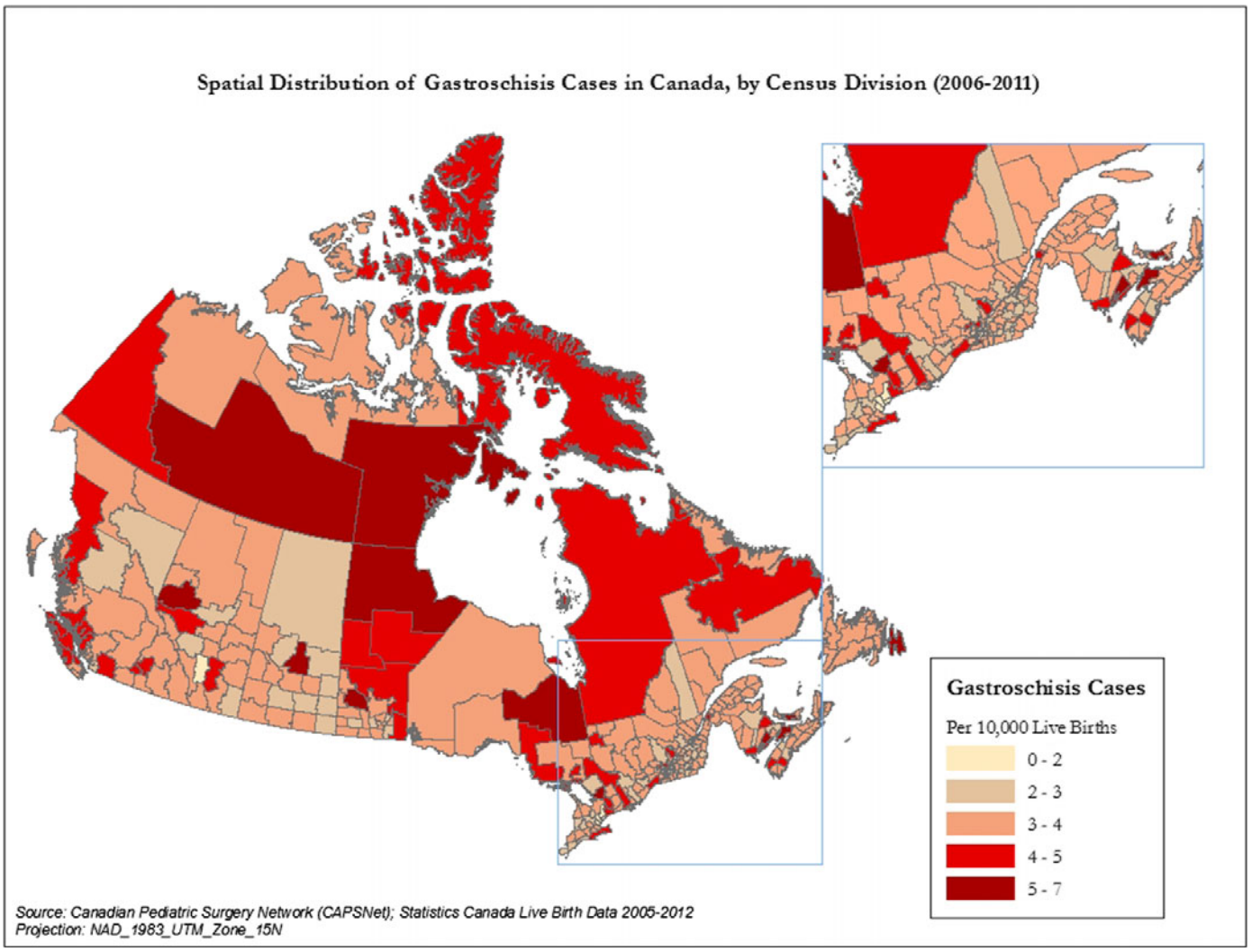

Figure 1. Spatial distribution of gastroschisis cases in Canada by census division, 2006–2011

123 per 100,000 in Nunavut. However, after adjusting for the underlying age of pregnant populations in each province/territory, some of these rates changed, with Nunavut and the Northwest Territories rates lowering to 36 and 68 per 100,000 respectively.

Figure 1 demonstrates visually the spatial distribution of gastroschisis cases by census division (CD). The phenomenon of spatial clustering is suggested, with several CDs noted to have gastroschisis rates in the 4 to 7 per 10,000 live birth range.

Figure 2 demonstrates the application of LISA to CD areas. As can be seen, there are High-High clusters (areas of significantly high rates surrounded by other areas of significantly high rates), High-Low clusters (areas of significantly high rates surrounded by areas of significantly low ones), Low-High clusters (areas of significantly low rates surrounded by areas of significantly high ones), and Low-Low clusters (areas of significantly low rates surrounded by other areas of significantly low rates).

DISCUSSION

The recently and widely documented increase in incidence rates of gastroschisis has spurred interest in understanding the epidemiology of this birth defect, which remains a significant cause of infant morbidity and, less frequently, mortality. In view of the sustained, resource-intensive care required in caring for infants born with this birth defect,[23] efforts targeting optimization of care must continue; however there is an accompanying urgent need for a more precise understanding of the risk factors for occurrence, including potential environmental causation factors, which may offer geographic targets for primary prevention strategies.

This study is the first to look at geographic distribution of gastroschisis using a national, population-based dataset. Using maternal residence postal codes, gastroschisis cases were mapped to CDs; after adjustment for local live birth rates, it is clear that there are CDs with higher than expected gastroschisis rates distributed across the country.

Relatively little is known about the phenomenon of geographic clustering in gastroschisis. A recent study reported evidence of geographic clustering of gastroschisis births within two discrete geographic areas in the state of North Carolina.[20] In this study, gastroschisis cases and controls, geocoded by address of maternal residence, were assigned to a discrete geopolitical area (census block groups). The use of controls allowed maternal covariates (for example, race and ethnicity, smoking status) potentially associated

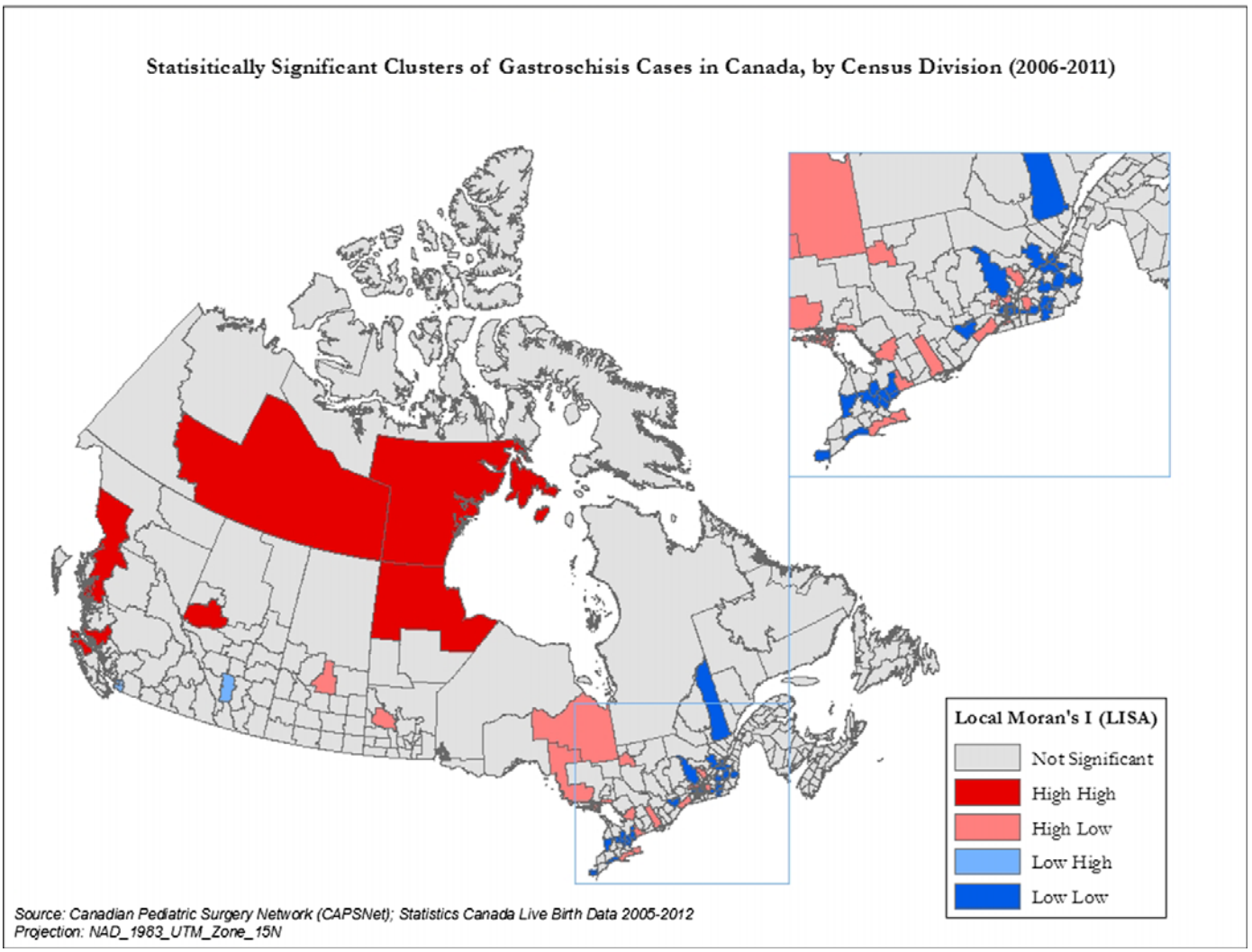

Figure 2. Cluster analysis of gastroschisis in Canada by census division, 2006–2011

with gastroschisis occurrence to be adjusted for in logistic regression models examining the independent relationship between geographic areas and the incidence of gastroschisis. Using a spatial scan technique which compared the observed and expected incidence of gastroschisis within elliptical windows distributed across the study area, combined with a calculated likelihood ratio (likelihood of finding the observed number of gastroschisis births within and outside the ellipse), two gastroschisis incidence clusters were identified. When covariates known to be associated with gastroschisis were included in logistic regression models, one of the spatial clusters lost predictive significance, while the other was weakened, yet remained significant.

When spatial clusters are identified, it is intuitive to hypothesize what phenomena might explain the occurrence of a cluster. One putative predictor is the impact of geographically centralized poor socio-economic conditions. This environment may expose women to greater psychosocial stress, or be a socio-economic proxy for risky maternal behaviours, including smoking, drinking alcohol or use of illicit drugs, all of which have been shown to be associated with increased prevalence of gastroschisis. Spatial clustering may also be the result of local environmental conditions (e.g., pollutants), which could increase the risk of a pregnancy complicated by gastroschisis. Building upon their geocoded observations of gastroschisis case clustering, the same investigators from North Carolina have integrated socio-economic variables from the US Census Bureau to estimate "neighbourhood"-level profiles of socio-economic determinants of health, including education, employment, poverty and racial composition.[24] Their study demonstrated a weak association between residence and lower SES neighbourhood, as measured by poverty and unemployment and the risk of having a gastroschisis-affected pregnancy.

Environmental teratogen exposure is another potential explanation of spatial clustering of birth defects. A study from Washington State looked at surface water agrichemical concentration and season of conception (winter, spring, summer or fall) as predictors of a gastroschisis-affected pregnancy.[17] Using a case-control methodology and a multivariate regression model to adjust for maternal covariates, investigators found that spring conception was significantly associated with a gastroschisis-affected pregnancy, while a trend towards a decreased risk of gastroschisis with increased distance from sites of higher

agrichemical (atrazine) concentration was observed. Occupational exposures, particularly exposures to polycyclic aromatic hydrocarbons, have also been linked to an increased incidence of gastroschisis in mothers older than 20 years.[25]

In our study, we have identified spatial variation at both the provincial/territorial as well as census-division level in Canada. The Yukon, Northwest Territories and Prince Edward Island were found to have higher rates of gastroschisis overall, as compared with other provinces/territories. Variation within provinces/territories at the CD level was also considered. Some CDs in Alberta, British Columbia, Manitoba, Northwest Territories, Ontario and Saskatchewan depict a higher prevalence of gastroschisis compared to other CDs. Comparing the spatial distribution of gastroschisis cases by census division (Figure 1) and the application of LISA by census division (Figure 2), many of the areas with either high or low prevalence of gastroschisis were found to be statistically significant clusters geographically. The cluster analysis suggests that there may be some coastal predilection for gastroschisis in Canada, with coastal British Columbia demonstrating pockets of geographic areas with increased prevalence compared to neighbouring communities (high-high clusters). In addition, areas in the Northwest Territories and Nunavut also displayed increased prevalence of gastroschisis. The cluster analysis, however, did not find statistical significance geographically for many of the eastern provinces, including Nova Scotia, Prince Edward Island, New Brunswick and Newfoundland & Labrador. Of particular interest, however, are areas that depict either high-low or low-high clusters, which can indicate spatial outliers. Some significant low-high clusters were found in the south portion of Alberta and British Columbia, indicating a lower prevalence of gastroschisis than in surrounding areas. In central Saskatchewan, southern Manitoba and across parts of Ontario and eastern Quebec, isolated areas of high prevalence (i.e., "hotspots") surrounded by areas of low prevalence were also found. Exposures to agricultural as well as oil and gas industry byproducts have been cited as potential risks. Further study will better delineate these relationships in Canada. Socio-demographic clustering also occurs in Canada with communities that differ significantly in terms of ethnicity, economics, and risk behaviours. As with previous studies, we have not seen clustering of gastroschisis cases in metropolitan areas. Whether the clustering of gastroschisis births in Canada is related to environmental factors, social factors or both, requires further study.

Limitations

There are a few limitations to the data and analysis used in this research. One is the low prevalence of gastroschisis, and the influence of population density on comparability of rates between the provinces and the less densely populated territories (Yukon, Northwest Territories, Nunavut), where the apparent rates may not be truly representative given the small denominator. Another limitation is the fact that, in calculating the prevalence of gastroschisis, we have included stillbirths and terminations of pregnancy in addition to live births (total prevalence), while Statistics Canada data estimates total births in the census division of interest using live births only. This method may lead to an overestimate of the "true" incidence of gastroschisis, since ideally we would have used all pregnancies (rather than only live births) as the true "denominator".

Caution should also be used in interpreting data presented in maps. While the maps illustrate differences across regions, they cannot be used solely to identify causal relationships, which we have emphasized in this discussion. Last, there are two sites that were missing some data during one year of the study time period (one in Alberta and one in Quebec). As a result, the number of cases for these provinces may be a slight under-representation of the actual prevalence.

CONCLUSIONS

Data from our study create an opportunity for further exploratory hypothesis testing, using spatial clustering as a framework for understanding maternal exposures and psychosocial experience within the environment of residence as potentially modifiable risk factors for the development of gastroschisis. There is clear evidence of spatial variation in the rate of gastroschisis across Canada. Future research should explore the role of area-based variables in these patterns to improve our understanding of the etiology of gastroschisis.

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RÉSUMÉ

OBJECTIFS : Le laparoschisis est une anomalie congénitale grave de la paroi abdominale associée à la mortalité et à une importante morbidité. Nos connaissances des facteurs à l'origine de cette malformation sont limitées. Nous avons cherché à décrire la variation spatiale de l'incidence du laparoschisis et à caractériser la structure spatiale de tous les cas de laparoschisis survenus au Canada entre 2006 et 2011. Plus précisément, nous avons voulu vérifier les différentes structures spatiales des régions géographiques et repérer les grappes significatives et leur emplacement.

MÉTHODE : La population étudiée comptait 641 cas de laparoschisis trouvés dans la base de données du Réseau canadien de chirurgie pédiatrique (CAPSNet), un fichier de données populationnelles de tous les cas de laparoschisis au Canada. Les cas ont été géocodés d'après le lieu de résidence de la mère. En utilisant les données de Statistique Canada sur les naissances vivantes comme dénominateur, nous avons calculé la prévalence totale du laparoschisis par province ou territoire et par secteur du recensement. Ces taux ont ensuite été cartographiés à l'aide d'ArcGIS. La détection des concentrations de cas a été effectuée à l'aide d'indicateurs locaux d'associations spatiales.

RÉSULTATS : Il existe une hétérogénéité spatiale importante des taux de laparoschisis au Canada, tant à l'échelle provinciale et territoriale qu'à celle des secteurs du recensement. Le Yukon, les Territoires du Nord-Ouest et l'Île-du-Prince-Édouard ont des taux globaux de laparoschisis plus élevés que les autres provinces et territoires. Plusieurs secteurs du recensement en Alberta, au Manitoba, en Saskatchewan, en Ontario, dans les Territoires du Nord-Ouest et en Colombie-Britannique présentent des grappes de laparoschisis, contrairement à leurs contreparties.

CONCLUSIONS : Il existe des preuves manifestes de variation spatiale des taux de laparoschisis au Canada. Les recherches futures devraient explorer le rôle des variables régionales dans cette configuration, afin d'améliorer nos connaissances de l'étiologie du laparoschisis.

MOTS CLÉS : analyse spatiale; laparoschisis; analyse en grappes; Canada