REGIONAL VARIATIONS IN THE PREVALENCE OF MAJOR CONGENITAL MALFORMATIONS IN QUEBEC: THE IMPORTANCE OF FETAL GROWTH ENVIRONMENT

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ABSTRACT

Background

Congenital anomalies are the consequence of a complex interaction between genetic predisposition and fetal environment. Based on the Congenital Anomalies Surveillance in Canada Report, between 1998 and 2007 the rate of congenital heart defects in Quebec was significantly higher than the Canadian average; no data on the overall prevalence of congenital anomalies for Quebec or data on regional variations in any province are available.

Objectives

To estimate the prevalence of major congenital malformations (MCMs) in all of the 17 administrative regions of Quebec.

Methods

Using data from the Quebec Pregnancy Cohort, we included infants if they were born between January 1, 1998 and December 31, 2008. MCMs were identified within the infant's first year of life using validated ICD-9 and ICD-10 codes. The rate of MCMs was calculated and stratified on Quebec's administrative regions.

Results

Among 152,353 eligible infants, the prevalence of MCMs was 36.6 (all rates were reported as per 1,000 live births). The regions with the highest rate of MCMs were Lanaudière (48.1), Laval (45.8), and Mauricie (45.1). Regions with the lowest rate were Outaouais (13.4), Côte-Nord (19.1), Abitibi-Témiscamingue (27.5), Gaspésie-îles-de-la-Madeleine (27.9), and Saguenay-Lac-Saint-Jean (28.9). Congenital heart defects (10.3) and musculoskeletal anomalies (12.6) were the most common. Laval had the highest rate of heart defects (16.1), and Lanaudière had the highest rate of musculoskeletal anomalies (22.0).

Conclusions

The central regions of Quebec had high rate of MCMs, whereas the relatively genetically homogenous peripheral regions of Quebec had lower rate of MCM, suggesting the importance of fetal growth environment in the etiology of MCMs in Quebec.

Key Words: *Major congenital malformations; Quebec pregnancy cohort; regional variations; founder effect; genetic predisposition; fetal growth environment*

Congenital heart defects are the most common congenital anomaly in newborns, and the most frequent causes of infant death from birth defects.[1,2] Based on the Congenital Anomalies Surveillance in Canada Report from 1998 to 2007,[3] the combined rate of congenital heart defects in Quebec was significantly higher than the Canadian average (~15 vs. 10 per 1,000 total births). However, in this report, there is no data for the overall prevalence rate of congenital anomalies for the province of Quebec, and there is no data on regional rates for any province. This information is particularly relevant to Quebec, as many congenital anomalies are presumed to be the consequence of a complex interaction between genetic predisposition and fetal environmental factors.[3-5] Indeed, the Quebec French Canadians are known for their high frequency of specific hereditary diseases, as they derive from a relatively small number of founders and the population expanded rapidly over the years in a context of relative isolation caused by geographic barriers and distinctive cultural/religious/ethnic identities.[6,7] However, the distribution of Mendelian disorders and the underlying mutations are uneven across regions.[8] In Saguenay-Lac-St-Jean, a geographically isolated region of Quebec, some rare inherited disorders, such as autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), cystic fibrosis, vitamin D-dependent rickets and lipoprotein lipase deficiency, have a fairly high carrier frequency.[9] On the other hand, there is no evidence of a high frequency of any genetic disorders in the western part of Quebec, suggesting a geographic stratification of the founder's effect.[10] There is only one study that examined the regional disparities in certain congenital anomalies, such as heart defects, limb reduction and hydrocephalus, in Quebec during 1989-1995.[11] The regional comparisons did not yield clear trends as there is variability in the measurement of data within each region.[11] Therefore, the purpose of this study is to estimate the rate of major congenital malformations (MCMs) for 11 organ system categories and in all of the 17 administrative regions of Quebec during the years 1998-2008, and to determine whether certain regions contributed more to the higher prevalence estimates reported for some congenital malformations in Quebec, such as congenital heart defects,[3] limb deficiency defects[3,11] and renal agenesis.[11]

METHODS

Data Sources

This study was performed within the Quebec Pregnancy Cohort. Details about this cohort have been described previously.[12,13] In brief, the Quebec Pregnancy Cohort was built using a patient unique identifier with the linkage of four administrative databases: health and medication insurance plan of the Régie de l'assurance-maladie du Québec (RAMQ), Med-Echo's hospital admission and discharge summary databases, birth and death registry administered by the Institut de la statistique du Québec (ISQ), and the Ministère de l'éducation, des loisirs et du sport (MELS) database. The RAMQ database provides prospectively collected data on all filled prescriptions, physician-based diagnosis, physician and emergency department visits, medical services dispensed, admissions to hospital, and characteristics of health care providers and patients in the province of Quebec. The Med-Echo database

contains information on hospitalizations; it also records gestational age (defined from the first day of the last menstrual period to the end of pregnancy, validated by ultrasound) for planned and spontaneous abortions, and deliveries. The ISQ provides demographic information on the mother, father, and newborn, as well as birth weight and gestational age for the live births and stillbirths. Finally, the MELS database provides information on the use of specialized services such as speech therapy for elementary school children. Data recorded in the RAMQ, Med-Echo, and ISQ have been validated[14,15] and used in the past for epidemiological research.[16-18]

Study Population

To be eligible for this study, infants had to be born alive between January 1, 1998 and December 31, 2008. If a woman had more than one infant for a given pregnancy, each infant was considered independently in the analysis. If a woman had more than one pregnancy, all pregnancies and infants were included in analyses. This study was approved by the ethics committee of the CHU Sainte-Justine. Linkage and access to information needed for the creation of the Quebec Pregnancy Cohort was authorized by the Commission d'accès à l'information du Québec.

Study Design

Within the Quebec Pregnancy Cohort, an ecological study was performed to estimate the rate of MCMs for 11 organ system categories in Quebec during 1998-2008. In addition, using either the municipality code or the city name assigned to each infant (provided by the ISQ database), geographical variations in the rates of MCMs were compared between all of the 17 administrative regions of Quebec.

Case Definition

Within the study population, we identified all cases of MCMs using validated ICD-9 and ICD-10 diagnostic codes.[19-21] Infants with MCMs were defined as if they received at least two diagnostic codes for the same category of MCMs at delivery or during the 12 months after delivery. Abortions (planned or spontaneous) and stillbirths were thus not included in this study. The MCMs were grouped into 11 organ system categories: central nervous system anomalies (ICD-9: 740–742; ICD-10: Q00–Q07); eye, ear, face and neck anomalies (ICD-9: 743–744; ICD-10: Q10–Q18); congenital heart defects (ICD-9: 745–746; ICD-10: Q20–Q24); circulatory system anomalies (ICD-9: 747; ICD-10: Q25–Q28); respiratory system anomalies (ICD-9: 748; ICD-10: Q30–Q34); cleft lip and/or palate (ICD-9: 749; ICD-10: Q35–Q37); digestive system anomalies (ICD-9: 750–751; ICD-10: Q38–Q45); urogenital system anomalies (ICD-9:752–753; ICD-10: Q50–Q56 and Q60–Q64); musculoskeletal anomalies (ICD-9: 754–756; ICD-10: Q65–Q79); chromosomal anomalies (ICD-9:758; ICD-10: Q90–Q99); and other anomalies.

Statistical Analyses

Descriptive statistics were used to estimate the rate of each organ system anomaly for the 17 administrative regions of Quebec. The MCMs rates for each organ system anomaly overall and for each of the 17 administrative regions are expressed as per 1000 live births and calculated by dividing the total number of MCMs cases by the total number of live births in the region multiplied by 1000. All statistical analyses were performed using SAS 9.1 (SAS Institute, USA).

RESULTS

Within the Quebec Pregnancy Cohort, 152,353 infants met the inclusion criteria and were thus included in this study. Among them, 5,581 infants were diagnosed with at least one MCMs. Therefore, the overall rate of MCMs in Quebec during the years 1998-2008 was 36.6 per 1,000 live births. The Nord-du-Quebec district had an extremely limited number of recorded live births, thus was excluded from the analysis. Table 1 summarizes the number and rates of MCMs in each organ system category overall and for the 16 administrative regions of Quebec. Figures 1-6 map the overall prevalence of MCMs, and the rates in 5 out of 11 organ system categories, including congenital heart defect, and circulatory, digestive, musculoskeletal, and nervous system anomalies for all Quebec regions.

TABLE 1 Number of cases, rates of MCMs overall and stratified by organ system categories and administrative regions of Quebec [n, (prevalence per 1,000 live births)]

			ORGAN SYSTEM DEFECT										
Regions	Total number of live births	Overall	Heart	Circulatory	Digestive	Musculoskeletal	Nervous	Respiratory	Cleft lip & palate	Urogenital	Eye, ear, face, neck	Chromosomal	Other
01 Bas-Saint-Laurent	4,409	143 (32.4)	42 (9.5)	7 (1.6)	10 (2.3)	49 (11.1)	14 (3.2)A	1 (0.2)	7 (1.6)	22 (5.0)	2 (0.5)	13 (2.9)B	11 (2.5)
02 Saguenay	6,086	176 (28.9)	38 (6.2)	14 (2.3)	11 (1.8)	57 (9.4)	9 (1.5)	7 (1.2)	11 (1.8)	26 (4.3)	5 (0.8)	14 (2.3)	18 (3.0)
03 Capitale-Nationale	11,890	508 (42.7)	98 (8.2)	31 (2.6)	26 (2.2)	161 (13.5)	33 (2.8)	31 (2.6)B	21 (1.8)	76 (6.4)A	7 (0.6)	60 (5.0)A	111 (9.3)A
04 Mauricie	5,916	267 (45.1)	79 (13.4)B	15 (2.5)	16 (2.7)A	115 (19.4)	17 (2.9)	16 (2.7)A	3 (0.5)C	28 (4.7)	4 (0.7)	7 (1.2)	12 (2.0)
05 Estrie	5,681	174 (30.6)	54 (9.5)	13 (2.3)	8 (1.4)	55 (9.7)	17 (3.0)B	14 (2.5)	6 (1.1)	28 (4.9)	5 (0.9)	6 (1.1)	10 (1.8)D
06 Montréal	56,600	2,209 (39.0)	710 (12.5)	136 (2.4)	107 (1.9)	629 (11.1)	132 (2.3)	87 (1.5)	52 (0.9)	333 (5.9)	93 (1.6)	62 (1.1)	360 (6.4)B
07 Outaouais	4,793	64 (13.4)C	20 (4.2)D	5 (1.0)D	4 (0.8)D	23 (4.8)D	5 (1.0)C	0 (0.0)C	4 (0.8)	6 (1.3)C	1 (0.2)D	5 (1.0)	1 (0.2)C
08 Abitibi-Témiscamingue	3,386	93 (27.5)	31 (9.2)	6 (1.8)	7 (2.1)	33 (9.7)	5 (1.5)	3 (0.9)	3 (0.9)	11 (3.2)	1 (0.3)	8 (2.4)	8 (2.4)
09 Côte-Nord	1,515	29 (19.1)D	5 (3.3)C	3 (2.0)	3 (2.0)	5 (3.3)C	3 (2.0)	2 (1.3)	1 (0.7)	6 (4.0)	1 (0.7)	2 (1.3)	6 (4.0)
11 Gaspésie	2,116	59 (27.9)	15 (7.1)	2 (0.9)C	3 (1.4)	23 (10.9)	3 (1.4)	2 (0.9)	4 (1.9)B	11 (5.2)	0 (0.0)C	1 (0.5)D	4 (1.9)
12 Chaudière-Appalaches	5,528	189 (34.2)	35 (6.3)	6 (1.1)	12 (2.2)	84 (15.2)	8 (1.4)	5 (0.9)	5 (0.9)	27 (4.9)	4 (0.7)	16 (2.9)	13 (2.4)
13 Laval	5,889	270 (45.8)B	95 (16.1)A	17 (2.9)B	6 (1.0)	90 (15.3)	8 (1.4)D	1 (0.2)D	7 (1.2)	37 (6.3)B	11 (1.9)B	4 (0.7)	20 (3.4)
14 Lanaudière	5,587	269 (48.1)A	68 (12.2)	20 (3.6)A	8 (1.4)	123 (22.0)A	13 (2.3)	7 (1.3)	16 (2.9)A	24 (4.3)	7 (1.3)	6 (1.1)	18 (3.2)
15 Laurentides	7,608	326 (42.8)	69 (9.1)	9 (1.2)	6 (0.8)C	155 (20.4)B	12 (1.6)	12 (1.6)	10 (1.3)	37 (4.9)	21 (2.8)A	4 (0.5)C	22 (2.9)
16 Montérégie	20,570	663 (32.2)	174 (8.5)	32 (1.6)	26 (1.3)	252 (12.3)	25 (1.2)	31 (1.5)	20 (1.0)	77 (3.7)	27 (1.3)	21 (1.0)	94 (4.6)
17 Centre-du-Québec	4,640	139 (30.0)	34 (7.3)	12 (2.6)	12 (2.6)B	57 (12.3)	5 (1.1)D	8 (1.7)	3 (0.6)D	15 (3.2)D	4 (0.9)	6 (1.3)	14 (3.0)
All of Quebec	152,353	5,581 (36.6)	1,568 (10.3)	329 (2.2)	265 (1.7)	1,913 (12.6)	309 (2.0)	227 (1.5)	173 (1.1)	764 (5.0)	193 (1.3)	235 (1.5)	722 (4.7)

Abbreviations: Saguenay: Saguenay-Lac-Saint-Jean, Gaspesie: Gaspesie-Iles-de-la-Madeleine. **A:** the highest prevalence rate; **B**: second highest prevalence rate; **C**: the lowest prevalence rate; **D**: second lowest prevalence rate

FIG. 1 Total Prevalence of Major Congenital Malformations in Quebec

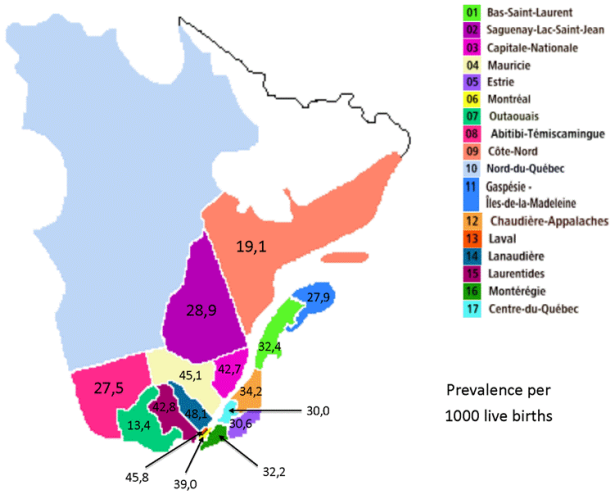


FIG. 2 Prevalence of Congenital Heart Defects in Quebec

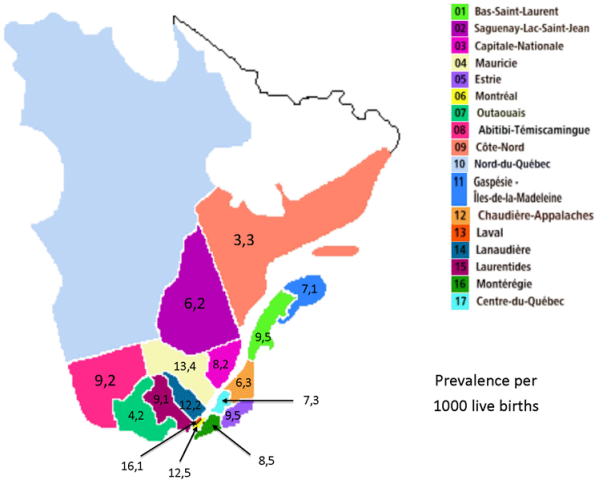


FIG. 3 Prevalence of Congenital Circulatory System Anomalies in Quebec

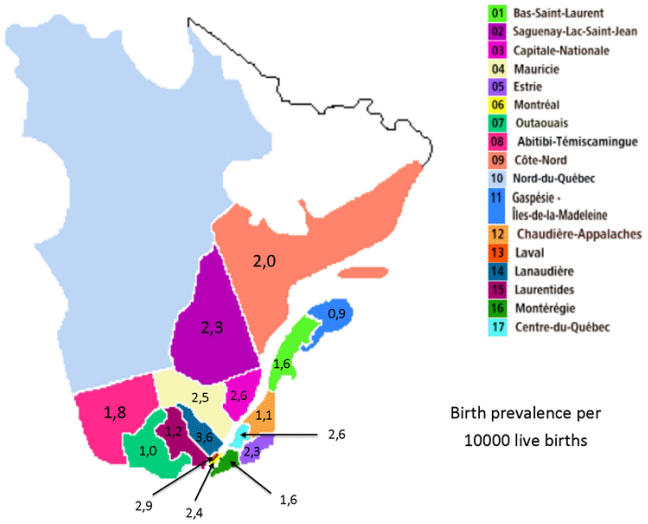


FIG. 4 Prevalence of Congenital Digestive System Anomalies in Quebec

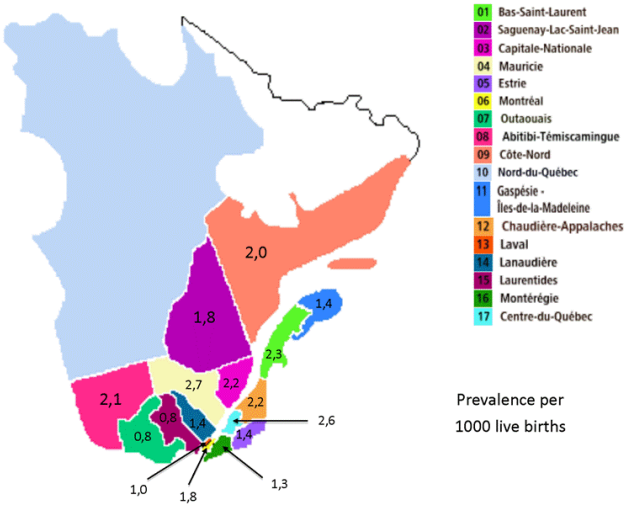


FIG. 5 Prevalence of Congenital Musculoskeletal System Anomalies in Quebec

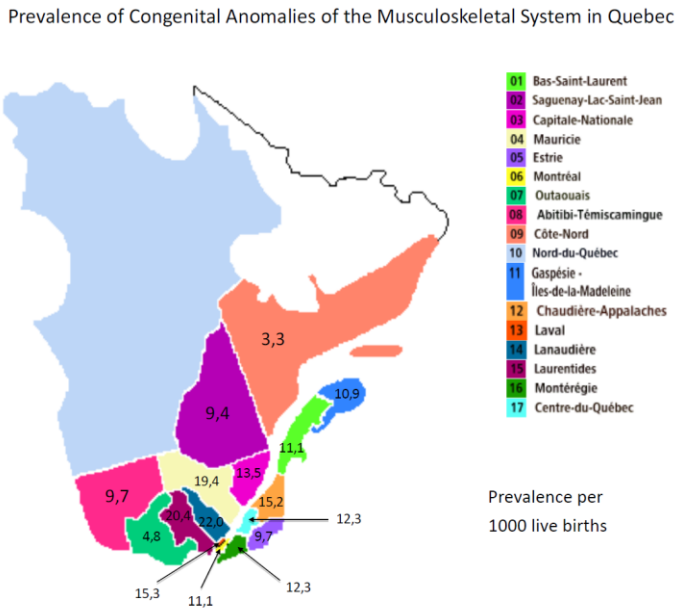
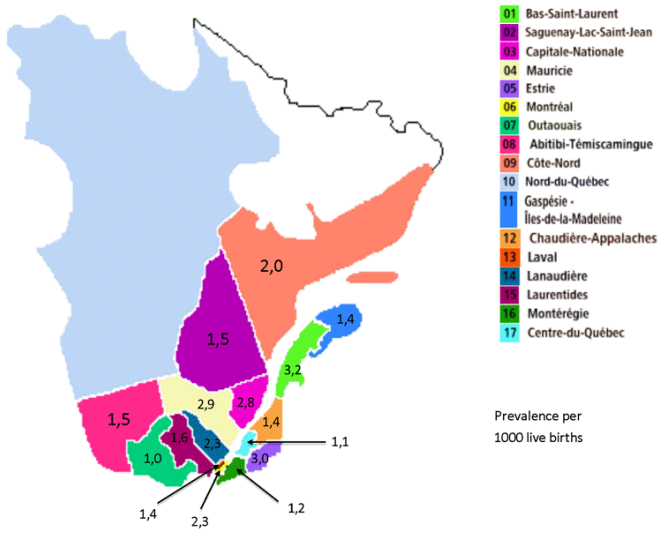


FIG. 6 Prevalence of Congenital Nervous System Anomalies in Quebec



Data from Table 1 and Figures 1-6 indicated that the central regions of Quebec had higher prevalence rate of MCMs than the peripheral regions of Quebec. Among the 16 administrative regions of Quebec, Lanaudière (a central region of Quebec) was at the top of the rank for the prevalence rates of MCMs in overall malformations, circulatory and musculoskeletal system anomalies, and cleft lip and palate. Similarly, Laval had the highest prevalence of heart defect, and the second highest rates for overall MCMs, urogenital system anomaly, and eye, ear, face and neck. Another central region of Quebec, Mauricie, was placed first for the prevalence of MCMs in digestive and respiratory system, and second in heart defect. Capitale-Nationale had the highest prevalence of MCMs in chromosomal and other anomaly system, and second highest in the respiratory system.

On the other hand, the peripheral regions of Quebec, Outaouais, was at the bottom of the rank for the prevalence rate of MCMs in 5 out of 11 organ system categories, and had the second lowest rates in 4 organ system categories. Another peripheral region, Côte-Nord, had the lowest prevalence rates of MCMs in 2 organ system categories, and had the second lowest overall MCMs rate. The peripheral region, Gaspésie-Îles-de-la-Madeleine, had the lowest rate of MCMs in circulatory system and in the eye, ear, face and neck anomalies.

DISCUSSION

Our findings are the first to detect a trend in the geographical variations concerning the rates of MCMs in Quebec. The central regions of Quebec, such as Lanaudière, Laval, Mauricie and Capitale-Nationale, are on top of the rank for the prevalence rate of MCMs in all of the studied organ system categories, whereas peripheral regions of Quebec including Outaouais, Côte-Nord, Gaspesie-îles-de-la-Madeleine, and Saguenay-Lac-Saint-Jean are at the bottom of the rank. These findings on the mapping of MCMs (Figure 1) are the opposite of the genetic disorder mapping in Quebec.[7,22,23] Indeed, regions with high prevalence of autosomal disorders, such as Saguenay-Lac-St-Jean, Gaspesie-îles-de-la-Madeleine and Côte-Nord, are characterized by geographic isolation as they were surrounded by tracts of unsettled land and lack of road access, which plays an essential part in forming the genetic homogeneity among the French Canadians of Quebec.[7,9] According to statistics from mid- to late-1980s, in the peripheral regions of Saguenay-Lac-St-Jean, the overall birth prevalence of recessive disorders was 1 per 207 among live births and the overall carrier rate was 1 per 7 inhabitants, whereas these conditions occur rarely in other populations.[9] Although the genetically homogeneous regions have higher rates of recessive autosomal disorders, it is unknown if the genetic homogeneity is associated with MCMs. Notably, certain environmental exposures increasingly modify the occurrence of congenital anomaly in the presence of predisposing genetic factors, such as higher risk of congenital heart defects in Down Syndrome children with mothers who smoke.[24] Thus, research on the interaction between genetic and environmental factors has been the main focus in the congenital anomalies etiologic study.[5] Many congenital anomalies are presumed to be the consequence of a complex interaction between genetic predisposition and fetal environmental factors.[3-5] In our study, the central regions of Quebec had high rates of MCMs; whereas, the genetically homogeneous peripheral regions of Quebec had lower rates of MCMs, suggesting the importance of fetal growth environment in the etiology of MCMs in Quebec.

Our findings are in line with Dolk's study as

they have compared the rates for defects with and without considering chromosomal abnormalities.[5] These rates clearly show that only a small portion of each defect is due to chromosomal abnormalities alone.[5]

In our study, the mean rate of congenital heart defect in Quebec was 10.3 per 1,000 live births in 1998-2008, which is consistent with Hoffman and Kaplan who reported that the rate of congenital heart defects in the USA is approximately 10 per 1,000 live births.[25] However, our estimate is lower than the mean that was recently reported by the Canadian Congenital Anomalies Surveillance System (CCASS), which was ~ 15.0 per 1,000 total births during 1998-2007.[3] The differences in the prevalence rates could be due to variation in data sources, case ascertainment and length of follow-up.[3,5] In addition to the MED-ECHO database, the CCASS also included stillbirths through Quebec Vital Statistics.[3] According to the Congenital Anomalies in Canada 2013 Report,[3] MCMs occurred in 8% to 10% of stillbirths in Canada. In addition, in our study, infants with MCMs received at least two diagnostic codes for the same category of MCMs within 12 months after delivery. Based on its report, the CCASS has shortened the length of ascertainment considerably from one year in 1998-2009 to 30 days after 2001 for all data derived from the Discharge Abstract Database (DAD).[3] This has resulted in some variations of the prevalence of MCMs over this time period.[3] However, in the CCASS report,[3] we could not find an actual follow-up length for the MED-ECHO database.[3] We thus assume that CCASS had the same follow up length for DAD and MED-ECHO databases as presumably CCASS managed both databases in the same manner. There are two reports available concerning the rates of MCMs in Quebec; however, they both reported on relatively common and easily diagnosed MCMs without discussing them in a systemic way.[3,11] Our study is the first to document the rate of MCMs for 11 organ system categories for all of the regions of Quebec. Among the three studies, congenital heart defect is the only category that had the same defined ICD-9 codes (745-746) between CCASS and our study.[3,11] This makes the rate of congenital heart defect as the only organ system category that may be compared to the two previous published studies. Based on the data, central regions like Laval, Mauricie and Montreal were found to constitute the largest portions of congenital heart defect in Quebec. In Quebec, 78% of the population lives in central urban regions; whereas, only 22% live in the peripheral rural regions.[26] The central regions of Lanaudière, Laval, Mauricie, and Capitale-Nationale, had the highest rates of MCMs. Urban living can be associated with different risk factors that could potentially lead to MCMs. Maternal age is a common risk factor for chromosomal abnormalities.[27] In the province of Quebec, based on the data from Quebec Birth Records Database from the year 1998 to 2000, women in rural areas have babies far younger than women who live in urban areas.[28] Compared to urban area women in the same age category, 64.9% more women in rural areas had babies between the ages of 20 to 24.[28] In contrary, urban area women had more than 40% more babies than women from rural areas in both the age categories of 40 to 44 and 45 to 49.[28] Older mothers are at higher risk of having or developing chronic medical conditions that can impact fetal and newborn health.[29] Indeed, maternal comorbidities such as obesity, hypertension, diabetes and thyroid disease, which are all known to impact major malformations in the newborn, are more prevalent in urban areas.[28,30] A study evaluating the general mental health of women of reproductive age concluded that rural women had fewer diagnoses of

depression or anxiety.[31] An antidepressant study in Australia indicated that total antidepressant utilization increased with age in both male and female subjects, and people living in remote area was among the category who used the least amount of antidepressants for all age groups.[32] A recent study has shown that some first-line treatment antidepressant use during the first trimester of pregnancy was associated with an increased risk of MCMs.[33] In the province of Quebec, compared to residents from urban areas, people living in rural areas have significantly more access to a family doctor (77.5% vs. 69.9% $P<0.05$) and institutionalized health care as indicated by higher general hospitalization rate (9.6% vs. 8.3% $P<0.05$).[28] In addition, environmental factors, air pollution, may also play a role in the variations of MCMs prevalence in Quebec.[3] There are environmental inequalities between urban and rural areas as a results of differential distribution of air pollution sources such as motor vehicles and local industry.[34]

The strengths of this study are its large population-based sample size, prospective data collection, validity of MCM codes, and availability of data according to region of birth. Limitations include that only live births were considered, potentially underestimating the rates calculated. Nevertheless, our methodology is similar to all other studies published on the subject thus far.[25] In addition, we did not have sufficient data for the administrative region of Nord-du-Quebec, hence limiting our ability to calculate the rate of MCMs for this region. The region of Nord-du-Quebec, which is primarily inhabited by Aboriginal people, had an extremely limited number of recorded live births in our database which can partly be explained by deliveries taking place in birthing centers or at home. Finally, we did not have data on Quebec residents giving birth outside Quebec, which can be relatively frequent for those residing in the region of Outaouais and Gaspésie–Îles-de-la-Madeleine, likely explaining their low overall birth defect rate.[35]

CONCLUSION

Congenital anomalies are presumed to be the consequence of a complex interaction between genetic predisposition and fetal environmental factors. The central regions of Quebec had high rates of MCMs; whereas, the relatively genetically homogenous peripheral regions of Quebec had lower rates, suggesting the importance of fetal growth environment in the etiology of MCMs in Quebec. Future studies are needed to investigate the association between risk factors and the geographic variation in the birth prevalence rates of MCMs in Quebec.

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