Maternal Risk Factors for Gastroschisis in Canada

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Background: Gastroschisis is a congenital abdominal wall defect that occurs in one per 2200 pregnancies. Birth defect surveillance in Canada has shown that the prevalence of gastroschisis has increased threefold over the past 10 years. The purpose of this study was to compare maternal exposures data from a national gastroschisis registry with pregnancy exposures from vital statistics to understand maternal risk factor associations with the occurrence of gastroschisis. Methods: Using common definitions, pregnancy cohorts were developed from two databases. The Canadian Pediatric Surgery Network database, a population-based dataset was used to record maternal exposures for women who experienced a gastroschisis pregnancy, while a contemporaneous, geographically cross-sectional "control" cohort of pregnant women and their exposures was developed from Canadian Community Health Survey data. Groups comparison of maternal risk factors was performed using univariate and multivariate logistic generalized estimating equation techniques. Results: A total of 692 gastroschisis pregnancies (from Canadian Pediatric Surgery Network) and 4708 pregnancies from Canadian Community Health Survey were compared. Younger maternal age (odds ratio, 0.85; 95% confidence interval, 0.83–0.87; $p < 0.0001$), smoking (odds ratio, 2.86; 95% confidence interval, 2.22–3.66; $p < 0.0001$), a history of pregestational or gestational diabetes (odds ratio, 2.81; 95% confidence interval, 1.42–5.5; $p = 0.0031$), and use of medication to treat depression (odds ratio, 4.4; 95% confidence interval, 1.38–11.8; $p = 0.011$) emerged as significant associations with gastroschisis pregnancies. Conclusion: Gastroschisis in Canada is associated with maternal risk factors, some of which are modifiable. Further studies into sociodemographic birth defect risk are necessary to allow targeted improvements in perinatal health service delivery and health policy.

Introduction

Gastroschisis (GS) is a congenital abdominal wall defect which results in the extrusion of the developing fetal intestines into the amniotic space. It is usually detected prenatally by maternal serum screening and ultrasound, and tends to occur as an isolated congenital anomaly. When a prenatal diagnosis of GS is made, arrangements are made for delivery at an obstetrical center that is functionally linked to a specialty pediatric hospital with the capability of providing surgical treatment after birth as well as essential neonatal intensive care. Survival following birth of an infant with GS exceeds 90%, however, survivors may require prolonged hospitalization in high intensity nurseries, which makes them among the most expensive of congenital anomalies to treat (Sydorak et al., 2002; Skarsgard et al., 2008). The specific cause of GS remains unknown, although the available evidence suggests interactions of multiple maternal risk factors lead to occurrence.

The Public Health Agency of Canada has documented a threefold rise in prevalence of GS over the last 10 years, to approximately 1 per 2200 births (Moore et al., 2013). A similarly observed increase in GS prevalence has been made in many other countries, including the United States and several European nations (Laughon et al., 2003; International Clearinghouse for Birth Defects Surveillance and Research, 2009; Langlois et al., 2011), prompting references to a "Gastroschisis Epidemic" (Kilby, 2006; Mastroiacovo et al., 2006; Keys et al., 2008). Epidemiologic studies of causation of GS have emerged from single state/region/country birth defect registries, to pooled data from a network of population-based congenital anomaly reporting registries, all with an intent to better understand modifiable risk factors for GS.

Since 2006, the Canadian Pediatric Surgery Network (CAPSNet) has collected standardized pre and postnatal data on all cases of GS admitted to each of the 17 hospitals in Canada that provide specialty pediatric care for birth defects. The collected data include maternal demographic (age, home postal code) and exposures (e.g., smoking, alcohol, recreational drug use) data for all GS pregnancies. The purpose of this study was to explore the association between maternal factors and GS in Canada by comparing maternal exposures data for GS cases identified in CAPSNet with household exposures data for a geographically "cross-sectional" group of pregnant women from a Canadian Vital Statistics database.

Materials and Methods

The two primary data sources for this study consisted of the CAPSNet registry, and the Canadian Community Health Survey (CCHS, which is administered by Statistics Canada),

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a cross-sectional survey which collects information related to health status and health determinants of Canadians at the household level, across all geographic regions (dissemination areas) in Canada (Canadian Community Health Survey [CCHS], 2014). Through integration of data from these two sources, we were able to develop health and maternal exposure risk profiles of mothers who gave birth to infants with GS (from CAPSNet), to pregnant women sampled from the CCHS. The variables that were consistently collected across the two data sources include: history of alcohol, tobacco, marijuana, cocaine, methamphetamine and heroin use during pregnancy, history of diabetes (type 1, type 2, or gestational), use of depression medication during pregnancy, and use of folic acid during pregnancy.

CAPSNet

The CAPSNet consists of the 17 perinatal/surgical centers that provide population-based pre- and postnatal care for GS in Canada (The Canadian Pediatric Surgery Network [CAPSNet], 2014). The CAPSNet registry was designed specifically for outcomes research and contains rigorously defined fields that allow discrimination of risk variables and treatment, as well as relevant clinical outcomes from the birth hospitalization to death or discharge. Data are collected from maternal and infant charts by trained abstractors using a customized data entry program with built-in error checking and a standard manual of operations and definitions. Abstracted prenatal information details maternal risk variables including demographics (postal code of residence), prenatal exposures including smoking, alcohol, and a variety of nonprescription drugs; medical comorbidities, quantitative ultrasound and other prenatal diagnostic data, and information on all pregnancy outcomes including stillbirths. All data collection is "observational" and is not used to influence the care of any individual patient.

Data from each CAPSNet center are de-identified and transmitted electronically to a centralized repository for cleaning, quality assurance and storage. Thereafter, the aggregate dataset is overseen by a research coordinator and a geographically representative, multidisciplinary steering committee comprised of pediatric surgeons, neonatologists, maternal-fetal medicine specialists, and an epidemiologist. Aggregate data use for research purposes is enabled by inter-institutional data sharing agreements, and requires that each CAPSNet center maintain institutional review board approval for data collection. Aggregate data release requires project-specific institutional review board approval from the principal investigator's institution, and complies with Health Information Portability and Accountability Act (HIPPA) requirements.

CCHS

CCHS is a cross-sectional household survey administered by Statistics Canada on an annual basis (before 2007 the survey was conducted in alternate years). The CCHS survey of 65,000 Canadians per year, targets persons aged 12 years or older who are living in private dwellings in the ten provinces and the three territories. Persons living on Indian Reserves or Crown lands, clientele of institutions, full-time members of the Canadian Armed Forces, and residents of certain remote regions are excluded from this survey. The sampling method ensures that all provinces' health regions (provincially designated health service areas) are sampled in proportion to the size of their respective populations.

The CCHS covers approximately 98% of the Canadian population aged 12 or older, and collects information related to health status, health care usage, and health determinants. These data can then be used to estimate, on a health regional basis, potential relationships between health outcomes and economic, demographic, occupational, and environmental factors. Ultimately, the data are meant to provide a better understanding of the health of Canadians and inform public policy, through health surveillance and the facilitation of population health research.

Study Design

This study used a cross-sectional design. In this design, the GS (case) sample consisted of all mothers identified from the CAPSNet database between 2006 and 2012, who had a GS pregnancy resulting in a live birth, stillbirth or termination of pregnancy, while the non-GS (control) sample consisted of all pregnant mothers responding to the CCHS surveys (Cycle 1.1 [2001], Cycle 2.1 [2003], Cycle 3.1 [2005], CCHS 2007, and CCHS 2010). Although CCHS data do not differentiate women whose pregnancy was or was not complicated by GS (or any other birth defect), it is assumed that the CCHS cohort represents a reasonable control group because the sample is large and the overall birth defect rate is known to be rare, and because controls misclassification causes bias toward the null for the risk factors.

The comparison variables of interest between cases and controls are summarized in Table 1. Definitions of "exposure" in both databases included any use, on at least one occasion of the listed substances, during a time when the woman was pregnant, whether known or unknown (Canadian Pediatric Surgery Network, 2013). A coincident history of diabetes, could mean that the woman had preexisting diabetes (type 1 or 2) diagnosed by a health professional or had gestational diabetes requiring medication or dietary modification. A history of depression requiring medication meant that the woman had a mood disorder diagnosed by a health professional and received antidepressive medication at any time in CAPSNet, (or within past month for CCHS), for any duration during her pregnancy. Folic acid use meant that the woman used a multivitamin containing folic acid before or upon realization of

TABLE 1. *CCHS and CAPSNet Variables Definitions*

	CCHS questions	CAPSNet data definitions[a]
Alcohol	Did you drink any alcohol during your last pregnancy? 1 Yes 2 No	Record if any alcohol use during pregnancy
Cigarette smoking	Did you smoke during your last pregnancy?[b] 1 Yes 2 No During your last pregnancy, did you smoke daily, occasionally or not at all?[c] 1 Daily 2 Occasionally 3 Not at all	Record if cigarettes were smoked during this pregnancy. If unknown or if no cigarettes were smoked during pregnancy, leave the box unchecked.
Marijuana	Have you used marijuana in the past 12 months? 1 Yes 2 No	Record whether or not the mother used any of the following during this pregnancy.
Cocaine	Have you used cocaine or crack in the past 12 months? 1 Yes 2 No	Marijuana Cocaine Methamphetamine or crystal meth
Methamphetamine	Have you used speed (amphetamines) in the past 12 months? 1 Yes 2 No	Heroin: includes methadone
Heroin	Have you used heroin in the past 12 months? 1 Yes 2 No	
History diabetes	Do you have diabetes? 1 Yes 2 No	Record the mother's status as a diabetic during this pregnancy. None Pre-existing DM diagnosed prior to conception Gestational diabetes Unknown
Depression meds	In the past month, did you take anti-depressants such as Prozac, Paxil or Effexor?: 1 Yes 2 No	Record use of antidepressants during this pregnancy: includes selective-serotonin reuptake inhibitors (SSRI) (i.e. Zoloft, Paxil or Prozac)
Folic acid	Did you take a vitamin supplement containing folic acid before your pregnancy, that is, before you found out that you were pregnant? 1 Yes 2 No	Record whether the mother has been taking regular prenatal vitamins during this pregnancy. None: no folic acid nor prenatal vitamins taken before the start of the second trimester. Folic acid: initiated prior to pregnancy or within the first trimester. Vitamins: initiated prior to pregnancy or within the first trimester Unknown

[a]From CAPSNet Abstractors' Manual vol 5.1.0, April 2013.
[b]Question from CCHS 1.1.
[c]Question from CCHS 2.1, 3.1, 2007, 2010.

her pregnancy. Age was estimated from maternal date of birth, as reported through both datasets, and was analyzed as a continuous variable. Geographic location of home residence was assigned using dissemination area (DA), a small, relatively stable geographic unit composed of one or more adjacent dissemination blocks. It is the smallest
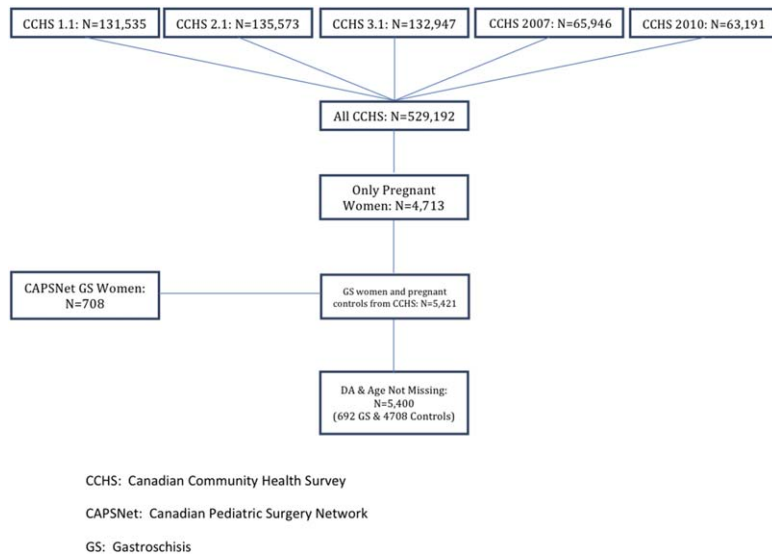
FIGURE 1. *Inclusion/exclusion flow diagram of patients analyzed in this study.Patients were collected from five cycles of the CCHS (1.1, 2.1, 3.1, 2007 and 2010). Patients who were pregnant during the time of the survey were included. The CAPSNet registry was used to identify women who had gastroschisis pregnancies between 2006 and 2012, and those with complete data were included.*

standard geographic area for which all census data are disseminated within Canada, and can be assigned using the Postal Code Conversion File software (Wilkins and Khan, 2010).

Initially, we intended to perform a 1:1 matched case control study where mothers were matched on age (a known GS risk factor) and DA, which would have allowed us to control for some predisposing environmental factors. When analysis was completed under the proposed design many associations between categorical risk factors and outcome of a GS pregnancy had low counts in some cells of the contingency tables. As a result, these data could not be released from Statistics Canada due to anonymity concerns and an alternative design was necessary.

STATISTICAL ANALYSIS

To avoid issues related to low cell counts, we chose not to match based on any demographic variables a priori. Rather we treated GS mothers and CCHS controls as being "clustered" within DAs and used logistic generalized estimating equation methods to account for this design feature. Moreover, we treated maternal age, (a known risk factor for GS occurrence) as a covariate in each model and estimated the adjusted odds of a GS birth, as a function of other hypothesized maternal risk factors after controlling for age. Where sample size allows we have summarized the association between maternal factors (all categorical variables) and GS occurrence using contingency tables.

Results

The process of deriving the case (GS pregnancies from CAPSNet) and control (non-GS pregnancies from CCHS) maternal cohorts is illustrated in Figure 1. After exclusions for incomplete data there were a total of 692 GS pregnan-

cies (from CAPSNet) and 4708 "control" pregnancies from CCHS.

The 692 GS mothers came from a total of 465 DAs and the 4708 control mothers came from a total of 1285 DAs. The mean age of the GS mothers was significantly lower than that of the controls (23.64 years; SD = 4.79 years vs. 28.84 years; SD = 6.11 years; $p < 0.0001$). When maternal age was interrogated as a predictive variable using bivariate and multivariate generalized estimating equation models, it emerged as independently predictive of the occurrence of a GS pregnancy (odds ratio [OR], 0.85; 95% confidence interval [CI], 0.83–0.87; $p < 0.0001$).

The relationships between maternal risk factors during pregnancy and the occurrence of GS are summarized in Tables 2 and 3. Table 2 displays 2x2 tables, estimated odds ratios, 95% confidence intervals and p-values associated with a variety of maternal substance exposures during pregnancy, folic acid use, depression medication use or a history of diabetes. Due to low cell counts, exposures data for cocaine, heroin, and methamphetamine were suppressed, and so an aggregate variable (any illicit drug use inclusive of marijuana) was created. Table 2 suggests that exposure to alcohol, tobacco, marijuana, illicit drugs or medication for depression during pregnancy, as well as a history of diabetes increases the likelihood of a GS pregnancy. Conversely, the use of folic acid appears to be protective against a GS pregnancy.

Given the awareness of young maternal age as a risk factor for GS, age adjustment was performed in the logistic generalized estimating equation risk modeling, as summarized in Table 3. After adjustment for maternal age, the association between maternal exposures to cocaine and marijuana individually, (and illicit drugs collectively) and the occurrence of GS persists. In the multivariate model, the composite "illicit drug" variable, emerges as a

TABLE 2. *2 x 2 Contingency Tables with Odds Ratios, 95% Confidence Intervals, and p-Values Describing the Relationship between the Association between Maternal Risk Factors and the Occurrence of a Gastroschisis Pregnancy*

	GS (*N*, %)	Controls (*N*, %)	Odds ratio	95% CI	*p*-Value
Alcohol					
Yes	44 (7.02)	203 (4.36)	1.66	1.18, 2.32	0.0031
No	583 (92.98)	4454 (95.64)			
Tobacco					
Yes	231 (33.38)	610 (13.06)	3.34	2.79, 3.99	<0.0001
No	461 (66.62)	4061 (86.94)			
Marijuana					
Yes	78 (11.27)	55 (1.56)	8.03	5.63, 11.46	<0.0001
No	614 (88.73)	3477 (98.44)			
Cocaine					
Yes					
No					
Methamphetamine					
Yes					
No					
Heroin					
Yes					
No					
Any illicit drug					
Yes	92 (13.29)	57 (1.61)	9.35	6.64, 13.15	<0.0001
No	600 (86.71)	3475 (98.39)			
History diabetes					
Yes	19 (2.75)	56 (1.19)	2.34	1.39, 3.98	0.0011
No	672 (97.25)	4651 (98.81)			
Depression meds					
Yes	22 (3.18)	26 (0.70)	4.65	2.61, 8.30	<0.0001
No	670 (96.82)	3544 (99.30)			
Folic acid					
Yes	134 (19.36)	1289 (27.83)	0.62	0.51, 0.76	<0.0001
No	558 (80.64)	3342 (72.17)			

Empty cells, suppressed due to low counts.

significant predictor of GS occurrence. Similarly, although alcohol exposure remained predictive after age adjustment, its predictive association with GS occurrence disappeared with multivariate analysis. The other significant variable change associated with age-adjustment was the loss of the apparent protection associated with folic acid use.

Younger maternal age, smoking (OR, 2.86; 95% CI, 2.22–3.66; $p < 0.0001$), a history of diabetes (OR, 2.81; 95% CI, 1.42–5.5; $p = 0.0031$), history of illicit drug use (OR, 3.54; 95% CI, 2.22–5.63; $p < 0.0001$), and use of medication to treat depression (OR, 4.4; 95% CI, 1.38–11.8; $p = 0.011$) remained independently predictive of GS occurrence.

Discussion

Gastroschisis is among the most common structural birth defects, and its cause remains unknown. The phenomenon of increased prevalence has been observed in several jurisdictions, and continues to be a stimulus for epidemiologic evaluation of risk factors, both maternal (physiological, teratogens, socioeconomic) and environmental (Torfs et al., 1994; Reefhuis and Honein, 2004; Rittler et al., 2007; Castilla et al., 2008; Salemi et al., 2009; Waller et al., 2010; Agopian et al., 2013).

The most widely observed association in GS pregnancy occurrence is its inverse relationship with maternal age. The risk seems to be highest in the teenage cohort. Aggregate data from EUROCAT (a consortium of birth defect registries which combines registry data from 23 countries) report a relative risk of 7.0 in the under 20 age cohort, and a RR of 2.4 in the 20 to 24 age cohort, compared with the age 25 to 29 reference group (Reefhuis and Honein, 2004). While a strong association with maternal age is certain, what is less clear is whether the increased prevalence of GS is due exclusively to an increased prevalence within the teenage mother population, or to a GS prevalence increase across all maternal age strata (Kazaura et al., 2004; Loane et al., 2007). Regardless of the exact nature of this association, the relationship between maternal age and GS should be factored in to all studies of GS epidemiology, with analyses of all putative risk factors being subject to age-adjustment.

Several epidemiologic studies of causation suggest a moderate risk of GS associated with smoking during pregnancy (Haddow et al., 1993; Draper et al., 2008; Feldkamp et al., 2008), and data from Canada identify a higher rate of smoking during pregnancy in mothers with GS (Weinsheimer et al., 2008). Not only is there a maternal smoking association with GS prevalence, there is also an association with clinical outcome, with GS infants of smoking mothers having more severe bowel injury at birth (Weinsheimer et al., 2008; Brindle et al., 2012). In addition to smoking, illicit drug use is another purported risk factor for GS, with cocaine, marijuana, and methamphetamine observed to have a significant age-adjusted association with GS occurrence (Draper et al., 2008; Weinsheimer et al., 2008; Brindle et al., 2012).

The current study provides further insight into GS epidemiology through integration of a contemporary, Canadian population-based GS dataset with Vital Statistics data from a cross-sectional, representative cohort of pregnant mothers from the Canadian Community Health Survey. Critical to the accuracy and reliability of this dataset

TABLE 3. *Bivariate, Age-Adjusted, and Multivariate Logistic Regression Models Evaluating Risk Factor Prediction of a Gastroschisis Pregnancy*

	Bivariate logistic gee model			Age-adjusted logistic GEE model			Multivariate logistic GEE model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	0.84	0.83, 0.86	<0.0001	—	—	—	0.85	0.83, 0.87	<0.0001
Alcohol	1.65	1.20, 2.29	0.0023	1.67	1.22, 2.30	0.0016	0.82	0.57, 1.18	0.2885
Tobacco	3.32	2.77, 3.98	<0.0001	2.53	2.08, 3.06	<0.0001	2.86	2.22, 3.66	<0.0001
Marijuana	7.94	5.50, 11.48	<0.0001	4.58	3.05, 6.90	<0.0001	—	—	—
Cocaine	11.32	5.10, 25.13	<0.0001	8.02	3.41, 18.83	<0.0001	—	—	—
Methamphetamine	2.90	0.83, 10.15	0.0950	1.16	0.32, 4.21	0.8236	—	—	—
Heroin	10.05	1.88, 53.79	0.0070	5.39	0.73, 39.87	0.0990	—	—	—
Any illicit drug	9.24	6.47, 13.21	<0.0001	5.46	3.69, 8.07	<0.0001	3.54	2.22, 5.63	<0.0001
History diabetes	2.29	1.39, 3.78	0.0011	3.40	1.97, 5.88	<0.0001	2.81	1.42, 5.57	0.0031
Depression meds	4.69	2.60, 8.45	<0.0001	6.09	2.97, 12.49	<0.0001	4.04	1.38, 11.80	0.0108
Folic Acid	0.62	0.51, 0.76	<0.0001	0.95	0.77, 1.17	0.6448	0.88	0.69, 1.14	0.3514

—, not used in multivariate model, rather combined in composite "illicit drug" variable.
GEE, general estimating equation.

integration, is the accuracy of case and control ascertainment, and equivalence of risk factor definitions. One of the limitations of birth defect registry ascertainment (for example EUROCAT) is the accuracy of discharge diagnosis abstraction from hospital charts. The diagnostic code for GS (International Classification of Disease, ICD-9 756.7) is shared with another congenital defect of the abdominal wall (omphalocele), which differs dramatically from GS and is frequently associated with genetic patterns of inheritance. The British Pediatric Association modification of ICD-9 is used by some registries, and allows differentiation of gastrochisis from omphalocele, however it is not used uniformly. The Canadian Pediatric Surgery Network (CAPSNet) database, on the other hand, is a research database, for which cases are ascertained by clinicians who are directly involved in either prenatal diagnosis or postnatal treatment of GS, which improves diagnostic accuracy considerably.

Our study reinforces the inverse relationship between maternal age and GS occurrence, as well as associations with maternal smoking and illicit drug use, which were both independently predictive of occurrence on multivariate logistic regression modeling. Although it was observed to be protective on univariate analysis, use of folic acid lost its predictive effect following adustment for maternal age. We also observed that treatment of depression with any anti-depressive medication was associated with an increased risk of GS (OR, 4.04; 95% CI, 1.38 = 11.8). A recent report from the National Birth Defects Prevention Study using a case control methodology, looked at the effect of periconceptual use of the anti-depressant venlafaxine on the occurrence of birth defects, and observed a statistically significant association with GS, after adjusting for maternal age and race (Polen et al., 2013). Conversely, two other studies looking at associations between selective serotonin-reuptake inhibitors in pregnancy did not demonstrate a significantly increased rate of common structural birth defects among exposed infants (Alwan et al., 2007; Louik et al., 2007). It is likely that an association between depression and/or its treatment and the occurrence of GS has many confounders, and, therefore, caution should be exercised in inferring a direct relationship in the absence of other supportive studies.

Our data identify a maternal history of pregestational type 1 or type 2 or gestational diabetes mellitus as being independently predictive of a GS pregnancy. While a relationship between pregestational/gestational diabetes and increased rates of several birth defects (specifically, cardiovascular defects), is well established, no specific association with human GS has been reported previously. Although the concept of abdominal wall malformations associated with a hyperglycemic state is plausible and supported by observations of GS in pregnant rats who were made diabetic by intraperitoneal streptozotocin (Padmanabhan and al-Zuhair, 1987–1988), this relationship is intuitively at odds with the observed protective effect of overweight or obese prepregnancy BMI on the risk of having a GS pregnancy (Lam et al., 1999; Waller et al., 2007; Stothard et al., 2009). A potential explanation for our findings is an underreporting of gestational diabetes in the CCHS cohort. A population-based study of rates of biochemically validated gestational diabetes in the province of Ontario, showed a doubling of age-adjusted rate from 2.7 to 5.6% between 1996 and 2010 (Feig et al., 2014), which is substantially higher than the rate of 1.2% observed in our CCHS cohort, and suggests the possibility

that a diagnosis of gestational diabetes was unknown to many pregnant women at the time they were surveyed. We are reluctant to ascribe much significance to this observation, other than to note its statistical significance, and suggest that future studies of GS epidemiology should evaluate this potential association further.

While this study has some unique strengths, it also has limitations. Combining unrelated sources of data (despite common definitions) for cases and controls raises concern over the comparability of maternal exposures between groups. Both data sources reflect self-reporting and are, therefore, subject to recall bias, and potentially, a reluctance to admit to risky behavior during pregnancy. Neither source specifically identifies pre or peri-conceptual exposure from exposure during pregnancy. The inquiry around timing of exposure in the CCHS database is variable, ranging from "past month" (antidepressant use), "during pregnancy" (alcohol, smoking), or "past 12 months" (illicit drugs, which could capture exposures before pregnancy). As previously acknowledged, the occurrence of birth defects, including GS within the "control" CCHS cohort cannot be excluded, yet we contend that it represents a reasonable control sample based on its size and the low birth defect rate.

Finally, the time periods reflected by the two databases are different: the CCHS controls represent an aggregate cohort from surveys done in 2001, 2003, 2005, 2007, and 2010, while the CAPSNet cases were accrued between 2006 and 2012). Another limitation is the inability to control for geographic factors (location of maternal residence). Although our initial intent was to undertake case/control matching by maternal age and dissemination area, the low counts in many of the DA cells meant that these data could not be released. We have, therefore, had to assume, for the purpose of this study, that GS occurs with the same prevalence across Canada, which we know is not the case, based on spatial mapping analysis of GS cases across Canada (K. Bassil, personal communication, 2014). We are also unable to make any observations of potential associations between maternal race and GS. In another CAPSNet study of GS epidemiology, we have observed a higher than expected prevalence of GS pregnancies in Aboriginal women, although maternal ethnicity does not emerge as independently predictive of occurrence (Brindle et al., 2012). The fact that the CCHS excludes Canadians living on Indian reserves means that Aboriginals may be underrepresented in our control group.

Future studies on causation of GS and other high impact structural birth defects will be enabled by our ability to integrate data from different sources, and speak to the necessity of having access to and linkages for a variety of clinical and administrative datasets. Improvements in perinatal health service delivery and health policy represent some of our greatest opportunities for outcome improvement for birth defects like GS.

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