Exposure to Gestational Diabetes Mellitus: Impact on the Development of Early-Onset Type 2 Diabetes in Canadian First Nations and Non–First Nations Offspring

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Type 2 diabetes is increasing in children worldwide, with Canadian First Nations (FN) children disproportionally affected. The prevalence of gestational diabetes mellitus (GDM) also is increasing. The objective of this study was to evaluate the impact of GDM exposure in utero and FN status on the subsequent risk of type 2 diabetes in offspring in the first 30 years of life.

RESEARCH DESIGN AND METHODS

In this population-based historical prospective cohort study, we used administrative databases linked to a clinical database to explore the independent association and interaction between GDM and FN status on the subsequent development of type 2 diabetes in offspring.

RESULTS

Among 321,008 births with a median follow-up of 15.1 years, both maternal GDM and FN status were independently associated with subsequent risk of type 2 diabetes in offspring in the first 30 years of life (hazard ratio 3.03 [95% CI 2.44–3.76; $P < 0.0001$] vs. 4.86 [95% CI 4.08–5.79; $P < 0.0001$], respectively). No interaction between GDM and FN status on type 2 diabetes risk was observed. FN status had a stronger impact on the development of type 2 diabetes in offspring than GDM.

CONCLUSIONS

GDM is an important modifiable risk factor for type 2 diabetes, and its prevention may reduce the prevalence of subsequent type 2 diabetes in offspring. This study adds unique and rigorous evidence to the global public health debate about the impact of GDM on the long-term health of offspring.

The prevalence of type 2 diabetes is increasing worldwide. Particularly alarming is the increase seen in children and young adults (1). Childhood-onset type 2 diabetes (<18 years of age) is a particular concern in Manitoba, Canada, where the incidence exceeds that of other Canadian jurisdictions by a factor of 10–20 (2,3). As seen around the world, indigenous children are disproportionally affected by type 2 diabetes in Manitoba, with First Nations (FN) children accounting for 90% of cases within our pediatric diabetes center (3).

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Gestational diabetes mellitus (GDM) is a state of glucose intolerance first detected during pregnancy (4). The prevalence of GDM varies among ethnic groups (5–9) and is higher in indigenous compared with nonindigenous women around the world (10). In Manitoba, the prevalence of GDM is three times higher in FN women than in non-FN women (9). GDM is a significant risk factor for subsequent development of type 2 diabetes in women (11–13) and increases the risk for type 2 diabetes in their offspring. In the Pima Indians (Akimel O'odham) of the southwestern U.S., maternal diabetes during pregnancy (exposure to either pre-GDM or GDM) is the strongest single risk factor for childhood-onset type 2 diabetes, accounting for >40% of type 2 diabetes in childhood (14). Similarly, in FN children in Manitoba, exposure to GDM increases the odds of childhood-onset type 2 diabetes fourfold compared with children not exposed to GDM (odds ratio 4.4 [95% CI 1.38–14.1]) (15). A systematic review published in 2010 of both prospective cohorts and retrospective studies found a trend for increased glycemic disorders, including type 2 diabetes, in offspring exposed to GDM in utero. However, the review did not identify any population-based studies to support previous clinic-based observations (16). Furthermore, no studies have determined whether the risk for early-onset type 2 diabetes after exposure to GDM differs between indigenous and nonindigenous offspring.

To address these gaps in the literature, we conducted a large, population-based, historical prospective cohort study of linked administrative databases that included all live births within the province of Manitoba between 1981 and 2007, with follow-up to 2011. The objective of this study was to evaluate the impact of GDM exposure in utero and FN status on the subsequent risk of type 2 diabetes in offspring in the first 30 years of life. We hypothesized that both GDM and FN status increase the risk. In addition, we describe the characteristics of offspring in whom type 2 diabetes developed by exposure to GDM and FN status.

RESEARCH DESIGN AND METHODS

Study Design, Databases, and Population of Interest

Since 1970, Manitoba Health has collected a complete standardized obstetric abstract form for all women who give birth in a hospital in the province. In Manitoba, 99% of all births occur in the hospital (17). Starting in 1981, the information from these abstracts has been incorporated into the Population Health Research Data Repository (henceforth called the Repository) at the Manitoba Centre for Health Policy at the University of Manitoba. The Repository contains linkable administrative databases, including physician claims, hospital discharge abstracts, vital statistics, and pharmaceutical prescriptions, for all registered individuals and uses scrambled personal health identification numbers. The Diabetes Education Resource for Children and Adolescents (DER-CA) database contains pediatric clinical care data for children <18 years of age with diabetes in Manitoba since 1986 and was used, together with the Repository, to ascertain diabetes status among offspring. Previous work has demonstrated a minimum ascertainment by the DER-CA for Manitoban children with type 1 diabetes of >95% and for all childhood-onset (<18 years of age) diabetes of >85% (18,19). A high ascertainment for childhood-onset diabetes in the Repository (>95%) has also been demonstrated (19). By linking these databases, we created a unique data set that includes maternal-child pairs studied from 1 April 1981 to 31 March 2011.

The study was approved by the Health Research Ethics Board at the University of Manitoba in accordance with the Declaration of Helsinki and the provincial Health Information Privacy Committee. Permission was obtained from the DER-CA for use of its database. Permission was also obtained for the use of the FN identifier in the Repository's status verification system from the Health Information Research Governance Committee of the Assembly of Manitoba Chiefs, the Department of Indigenous and Northern Affairs Canada, and the National Indian Registry System.

Exposures of Interest

The primary exposures of interest were GDM and FN status. GDM was defined as a diagnosis of GDM (through hospital abstract forms) at ≥21 weeks of gestation or any first-time incident diagnosis of diabetes (through hospital or physician claims data) at ≥21 weeks of gestation (20,21). Women with diabetes of any type at ≤20 weeks of gestation were excluded from the study to avoid the misclassification of pre-GDM. ICD-9-CM codes were used until 1 April 2004, and ICD-10-CA codes were used thereafter to define diabetes and GDM. FN status was verified in the database through the approved linkage with the National Indian Registry System database (99% reliability) for FN people living in Manitoba (22).

Outcomes of Interest

Incident type 2 diabetes among offspring in the first 30 years of life was the primary outcome of interest and was defined as one hospitalization or two physician visits in a 2-year period with a diagnosis of diabetes in the Repository or identified as having type 2 diabetes before age 18 years in the DER-CA database. The DER-CA database uniquely differentiates the types of diabetes in children based on reliable clinical and laboratory data, including diabetes-specific autoantibodies. Administrative claims data cannot differentiate between type 1 diabetes and type 2 diabetes diagnoses; therefore, to exclude type 1 diabetes diagnoses, all children with diabetes diagnosed at <7 years of age were excluded from the analysis because of the unlikelihood of their condition being type 2 diabetes. In addition, children >7 years of age with type 1 diabetes in the DER-CA database were censored. Young adults age 18–29 years with diabetes who had a hospital discharge claim of type 1 diabetes were also censored (total excluded or censored 83,728).

Definitions

Large for gestational age was defined as weight >90th percentile for gestational age, and small for gestational age was defined as <10th percentile for gestational age (23). Preterm birth was defined as a live birth at <37 weeks gestation (24). Income quintiles of mothers' regions of residence were defined as previously described (income quintile derived at time of delivery) (25).

Statistical Methods

Descriptive statistics were used to describe the characteristics of the cohort. ANOVA and Poisson regression analysis were used to investigate significant differences between exposure groups. Kaplan-Meier survival analysis was used to calculate the cumulative incidence rate for diabetes in offspring. Risk factors associated with the diagnosis of diabetes were assessed with Cox proportional

hazards regression models. Individuals who died or out-migrated before reaching their end point were censored. Whether FN status may modify the association between GDM and type 2 diabetes among offspring was assessed through an interaction term in the proportional hazards modeling. A diagnosis of diabetes before age 7 was considered to be non–type 2 diabetes; analyses of such offspring were restricted to those born between 1981 and 2004. All analyses were performed with SAS 9.3 statistical software.

To determine the role of the intrauterine hyperglycemic environment controlled for genetic susceptibility, sibling pairs discordant for GDM exposure were examined separately. We conducted the sibling pair analysis by means of a matched-pairs Cox proportional hazards model controlled for child's sex, mother's age, and birth weight.

RESULTS

A total of 410,677 deliveries were identified from the Repository during the 30-year study period. After excluding those with a mother with prepregnancy diabetes (n = 6,141), 404,736 deliveries from 214,028 women were included in this study (Fig. 1). We found that 11,906 (2.9%) of these pregnancies were complicated by GDM, with higher rates among FN women compared with non-FN women (6.7% vs. 2.2%; $P <$ 0.0001) (Fig. 1). After excluding offspring born after 2004 (<7 years of age at 2011), there were 321,008 births during the study period, with a median follow-up of 15.1 years (interquartile range 9.2–21.2) (Fig. 1). The median follow-up period did not differ significantly among the groups. Among FN offspring, the incidence of type 2 diabetes in the first 30 years of life was more than threefold higher for those exposed to GDM (1.82 per 1,000 person-years [95% CI 1.50–2.23]; $P <$ 0.0001) than for those not exposed (0.53 per 1,000 person-years [95% CI 0.48–0.58]; $P <$ 0.0001). Among non-FN offspring, incidence of type 2 diabetes was approximately double among those exposed to GDM (0.23 per 1,000 person-years [95% CI 0.15–0.36]; $P <$ 0.0001) compared with those not exposed (0.11 per 1,000 person-years [95% CI 0.10–0.12]; $P <$ 0.0001) (Table 1).

GDM exposure was significantly associated with increased birth weight in both the FN and the non-FN offspring (z = 23.65 and 11.42, respectively; $P <$ 0.0001), and the association was significantly stronger among those of FN heritage (χ^2 = 147.35; $P <$ 0.0001). Similarly, large for gestational age was more common in both FN (z = 30.97; $P <$ 0.0001) and non-FN (z = 28.04; $P <$ 0.0001) offspring exposed to GDM, but the effect was greater in FN offspring (χ^2 = 11.56; $P <$ 0.0007). In addition, small for gestational age was less common in those exposed to GDM in utero (z = −8.11 and −6.97 in FN and non-FN offspring, respectively; $P <$ 0.0001), with a greater effect in FN offspring (χ^2 = 17.91; $P <$ 0.0001). Premature birth was more common in offspring exposed to GDM, but this did not differ significantly between the FN and non-FN groups (z = 7.97 and 8.88; $P <$ 0.0001, respectively) (Table 1).

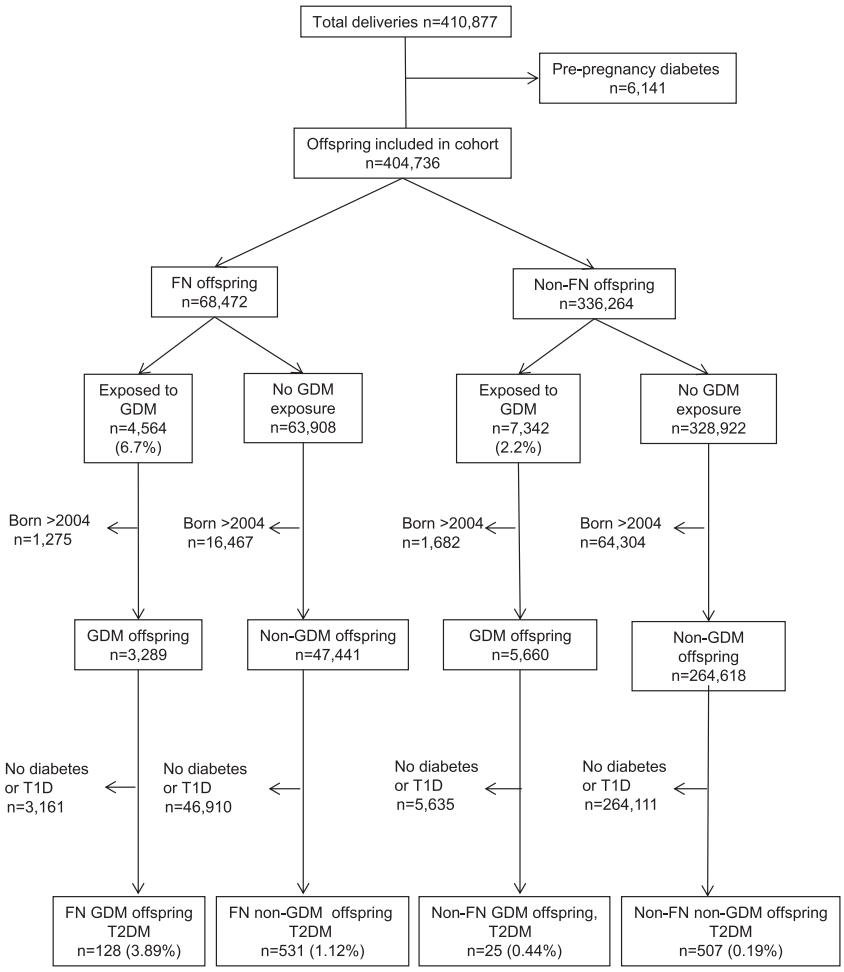

Figure 1—Cohort chart. T1D, type 1 diabetes; T2DM, type 2 diabetes mellitus.

Type 2 diabetes was diagnosed 6.5 times more frequently among FN offspring (659 of 50,730 [1.3%]) than among non-FN offspring (532 of 270,278 [0.20%]; $P <$ 0.0001) (Fig. 1). Type 2 diabetes among FN offspring with exposure to GDM was 8.8-fold greater than in non-FN offspring exposed to GDM (3.89% vs. 0.44%; $P <$ 0.0001) (Fig. 1). Similarly, type 2 diabetes among FN offspring without exposure to GDM was 5.9-fold greater than in non-FN offspring without GDM exposure (1.12% vs. 0.19%) (Fig. 1). Exposure to GDM preceded 128 of 659 (19.42%) cases of type 2 diabetes in FN offspring and 25 of 532 (4.70%) cases of type 2 diabetes in non-FN offspring (Fig. 1).

Maternal GDM and FN status were both associated with an increased risk of type 2 diabetes in offspring, and the risk for diabetes increased over time (Fig. 2). By age 25 years, the estimated prevalence of type 2 diabetes in FN offspring was 2.60% in those not exposed to GDM and 7.20% in those exposed to GDM. In non-FN offspring, the prevalence of type 2 diabetes by age 25 years was 0.45% in those not exposed to GDM and

Table 1—Description of offspring born between 1982 and 2004

	FN		Non-FN	
Outcome/factor	GDM (*n* = 3,289)	No GDM (*n* = 47,441)	GDM (*n* = 5,660)	No GDM (*n* = 264,618)
Birth weight (kg)	3.75 ± 0.65	3.50 ± 0.62	3.52 ± 0.62	3.43 ± 0.58
LGA	40.42	16.15	23.76	10.87
SGA	3.69	8.24	6.58	9.48
Preterm birth	10.53	6.72	9.17	6.18
Female sex	47.37	49.05	47.54	48.65
Rural resident	76.71	70.41	30.81	37.31
Birth year				
1982–1989	28.55	27.57	29.65	35.28
1990–1994	23.87	24.71	26.93	23.96
1995–1999	19.91	23.87	20.00	21.27
2000–2004	27.67	23.85	23.43	19.40
Income				
Quintile 1	66.61	60.53	21.91	17.81
Quintile 2	16.80	20.23	21.77	20.37
Quintile 3	8.57	8.37	20.88	21.10
Quintile 4	4.51	5.98	20.10	21.72
Quintile 5	3.51	4.89	15.32	19.01
Follow-up (years)	15.07 (9.79, 20.71)	15.23 (9.87, 20.50)	14.87 (8.75, 20.57)	15.37 (9.01, 21.42)
Type 2 diabetes	3.89	1.12	0.44	0.19
Incidence of type 2 diabetes (per 1,000 person-years)	1.82 (1.50–2.23)	0.53 (0.48–0.58)	0.23 (0.15–0.36)	0.11 (0.10–0.12)

Data are mean ± SD, %, median (interquartile range), or median (95% CI). Children born in 2005 or later could not reach the end point of development of type 2 diabetes because we defined first diagnosis of diabetes at age <7 years as type 1 diabetes. LGA, large for gestational age (>90th percentile); SGA, small for gestational age (<10th percentile).

1.1% in those exposed to GDM (Fig. 2). Type 2 diabetes was significantly more likely to develop in FN offspring exposed to GDM by 15 years of age than in FN offspring without an exposure to GDM ($P < 0.0001$). No significant interaction was found between GDM exposure and FN status; thus, FN status did not modify the risk of GDM exposure in pregnancy.

Cox proportional hazards regression models restricted to offspring who were born between 1981 and 2004 revealed that both maternal GDM and FN status were independently associated with subsequent risk of type 2 diabetes in offspring (hazard ratio [HR] 3.03 [95% CI 2.44–3.76] and 4.86 [95% CI 4.08–5.79], respectively; both $P < 0.0001$). Exposure to GDM was associated with a 3.23-fold increased hazard of type 2 diabetes in childhood in FN offspring and a 2.23-fold increased hazard in non-FN offspring compared with FN and non- FN offspring not exposed to GDM, respectively (Table 2). Both FN and non-FN female offspring had an increased risk for type 2 diabetes, although sex predilection was greater in FN offspring. Compared with children born in 1982–1989, type 2 diabetes was significantly more likely to develop in children born in later periods. Rural residence (at time of delivery) was associated with an increased risk for the development of diabetes in FN offspring (HR 1.52 [95% CI 1.21–1.92]; $P = 0.0004$) and a decreased risk in non-FN offspring (HR 0.81 [95% CI 0.67–1.00]; $P = 0.04$). Among non-FN offspring, the lowest income quintile was associated with an increased risk for type 2 diabetes in offspring compared with the highest income quintile. A similar

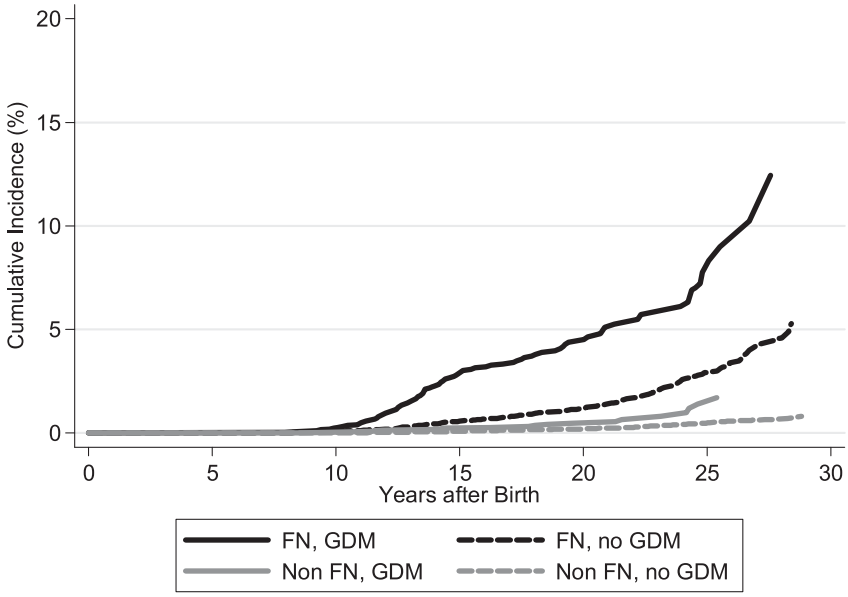

Figure 2—Risk of diabetes after pregnancy in offspring by GDM status of mother and FN heritage.

Table 2—HRs for type 2 diabetes in offspring

	Offspring			
	FN		Non-FN	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female sex	1.78 (1.48–2.14)	<0.0001	1.22 (1.02–1.47)	0.0316
LGA	1.00 (0.79–1.26)	0.9999	0.64 (0.44–0.93)	0.0188
SGA	1.07 (0.77–1.48)	0.7057	1.53 (1.18–1.98)	0.0013
Birth year				
1982–1989	Reference		Reference	
1990–1994	1.19 (0.94–1.51)	0.1427	1.41 (1.09–1.81)	0.0082
1995–1999	1.58 (1.16–2.15)	0.0040	1.79 (1.23–2.61)	0.0025
2000–2004	2.67 (1.33–5.36)	0.0056	1.59 (0.61–4.14)	0.3413
GDM in mother	3.23 (2.52–4.15)	<0.0001	2.23 (1.39–3.59)	0.0009
Rural residence	1.52 (1.21–1.92)	0.0004	0.81 (0.67–0.99)	0.0400
Income				
Quintile 1	1.53 (0.96–2.44)	0.0727	1.55 (1.15–2.09)	0.0042
Quintile 2	1.16 (0.70–1.92)	0.5663	1.11 (0.82–1.51)	0.5066
Quintile 3	1.70 (0.98–2.94)	0.0570	1.01 (0.74–1.37)	0.9767
Quintile 4	1.71 (0.97–3.02)	0.0622	0.83 (0.61–1.15)	0.2656
Quintile 5	Reference		Reference	

Offspring includes children born between 1982 and 2004 and followed until March 2011 or type 2 diabetes development or until they left the catchment area, whichever came first. (In this study, children <7 years were never classified with the end point of type 2 diabetes.) LGA, large for gestational age; SGA, small for gestational age.

association with income quintile at delivery was not found in the FN offspring (Table 2).

In offspring with type 2 diabetes diagnosed within the study period, a female predominance was seen, although there was no significant differences or interaction between those exposed or not exposed to GDM or by FN status. Age at diagnosis of type 2 diabetes was significantly lower in FN offspring exposed to GDM in utero (median 14.70 years) than in non-FN offspring exposed to GDM (median 17.55 years) and both FN and non-FN offspring not exposed to GDM (median 17.98 and 18.38 years, respectively; $z = -2.94$; $P = 0.005$).

Within the cohort, we identified 4,313 mothers who gave birth to at least one child who was not exposed to GDM and one child who was exposed to GDM (4,313 discordant sibling pairs, 8,626 offspring). Analysis of siblings discordant for GDM exposure revealed that the unexposed sibling was born before the exposed sibling in 73.6% of the pairs. Eighty-five sibling pairs were discordant for GDM exposure and type 2 diabetes status. When follow-up time was truncated so that both members of each pair had the same follow-up period, 57 pairs remained. Among these pairs, the risk for the development of type 2 diabetes in the first 30 years of life was similar (HR 0.43 [95% CI 0.18–1.04]). Among all the sibling pairs discordant for GDM exposure, the risk for the development of type 2 diabetes in the first 30 years of life was similar.

CONCLUSIONS

This large-scale population-based cohort database study evaluated the association of GDM and FN status on the subsequent risk of type 2 diabetes in offspring over a 30-year period in Manitoba. The unique linkage of large population-based administrative and clinical data sets as well as the careful epidemiological definition of GDM allowed for a careful differentiation of type 1 versus type 2 diabetes in offspring and reduced misclassification of GDM status due to prepregnancy diabetes. Although the study period encompassed several decades, no significant changes were found in place of FN and non-FN deliveries in Manitoba, with the majority occurring in a hospital (17,26).

Type 2 diabetes in the first 30 years of life developed in significantly more offspring exposed to GDM than in unexposed offspring. GDM and FN status were independently associated with the development of type 2 diabetes in offspring, and FN status did not modify the risk of type 2 diabetes in offspring exposed to GDM. FN status appears to have a greater impact than exposure to GDM on the subsequent development of type 2 diabetes in offspring at least within the first 30 years of life, the reasons for which are not known. The maximum follow-up of this cohort was 30 years (median ~15 years). The impact of genetics may play a more significant role in the development of relatively early-onset type 2 diabetes, and other early life exposures, including geographic and socioeconomic factors associated with FN status, may have been confounders. Longer-term follow-up will establish whether the apparent increased impact of FN heritage persists in offspring with diabetes diagnosed at an older age. The relative importance of various exposures may differ for those with type 2 diabetes diagnosed at a younger versus an older age. Overall, type 2 diabetes developed in 1.3% of FN offspring in Manitoba by age 30, a percentage that increased to almost 4% for FN offspring exposed to GDM.

Female offspring in all groups had an increased risk for the development of type 2 diabetes. This female predominance has been well described in childhood-onset type 2 diabetes, especially in indigenous populations (27–29). The reasons for this remain unclear and appear to be a unique feature of early-onset type 2 diabetes because sex differences in the older adult population are less significant.

The risk of type 2 diabetes progressively increased in offspring born after 1989 (Table 2), except for the youngest non-FN offspring. This finding may reflect the increasing prevalence of obesity in children and young adults during this period (30,31). This observation is particularly marked among FN children in Manitoba, where the prevalence of obesity is high and increasing. Overweight and obesity rates as high as 50% were reported in Manitoban FN school-aged children in the late 1990s (31). More recently, an obesity prevalence of >70% has been reported in a similar population (32). Obesity is a significant risk factor for the development of type 2 diabetes and is the most common clinical finding in children with type 2 diabetes (2,33). The increased risk of type 2 diabetes in offspring born after 1989 may also be influenced by the increasing rates of GDM in pregnancy over this period demonstrated in Manitoba and elsewhere (9,34).

In the current cohort, type 2 diabetes developed over a maximum follow-up period of 30 years in almost 4% of FN offspring exposed to GDM in utero. Of female FN offspring exposed to GDM in utero, type 2 diabetes developed in 5.9% by age 30 years. Given this young age of onset, the offspring of these women may be subsequently exposed to pre-GDM in utero, a potent risk factor for childhood-onset type 2 diabetes, thus perpetuating a vicious cycle (15,35).

In offspring with type 2 diabetes diagnosed by age 30, the mean age of diagnosis was significantly younger in FN offspring exposed to GDM than in all other subgroups. In children who develop type 2 diabetes prior to 18 years of age, a younger age of diabetes onset has been described in children exposed to pregestational diabetes in utero (36). Similarly, in the SEARCH for Diabetes in Youth (SEARCH) study, children with type 2 diabetes exposed to maternal diabetes in utero were younger at diagnosis than those who were not exposed. However, in the SEARCH study, exposure to diabetes in utero included both GDM and pre-GDM and was not separately evaluated (37). In the current study, the reasons for the younger age of onset associated with exposure to GDM in only FN offspring remain unclear. This may be an artifact of relatively small numbers, and larger studies will be required to confirm this observation.

In addition to GDM, rural residence was associated with an increased risk of type 2 diabetes in FN offspring. Although income quintile was not significantly associated with diabetes risk in FN offspring, the majority were in the lower two income quintiles; thus, the numbers in the upper quintiles were small. Significant income disparity exists between indigenous and nonindigenous people in Canada, with the average income 30% lower in indigenous people (38). Also well illustrated in Manitoban children from lower-income areas are poorer health outcomes than in those from higher income areas (39). Furthermore, almost 60% of FN people in Manitoba live on reserves, one-half of whom have no road access (40). These socioeconomic and geographic barriers that limit access to health care, healthy diet, and physical activity added to the profound impact of colonization on language, traditions, and culture interact in a complex manner to increase social inequity and the risk for type 2 diabetes in FN offspring.

The analysis of siblings discordant for exposure to GDM in utero did not demonstrate an increased risk for type 2 diabetes in the offspring exposed to GDM, which suggests that genetic or environmental factors other than the intrauterine effects of GDM contribute to the risk of type 2 diabetes. Among Pima Indians of the Gila River in the southwestern U.S., the risk of type 2 diabetes was significantly greater in siblings exposed to diabetes in utero than in those born before the mother developed diabetes (odds ratio 3.7) (35). Similarly, in the multiethnic American SEARCH study, in utero exposure to maternal diabetes was independently associated with type 2 diabetes in children (41). However, these reports included children exposed to both GDM and pre-GDM. In the current study, we carefully excluded those with pre-GDM exposure. To our knowledge, this report is the first of disease risk in siblings discordant for exposure to GDM only and suggests that the major impact of diabetes exposure in utero on subsequent type 2 diabetes in offspring is associated with pre-GDM exposure occurring in early gestation during organogenesis. This finding will require confirmation in future studies.

Although the study is strengthened by the population-level data and validated algorithms to assess both exposure and outcomes, several limitations of the design exist. First, the Repository does not contain data on maternal body weight or height; thus, we were unable to assess the impact of prepregnancy obesity or gestational weight gain on subsequent type 2 diabetes in offspring. In the SEARCH study, 19.7% of childhood-onset type 2 diabetes was independently attributed to exposure to maternal obesity during gestation (41). Second, the DER-CA database started in 1986. Misclassification of diabetes may have occurred in the small number of offspring age $<$18 years who were not referred to the DER-CA or for offspring in the Repository with diabetes diagnosed after age 18 years by physician claim. This small risk of misclassification is unlikely to have had a significant impact on the results. Also possible is that preexisting maternal diabetes was misclassified as GDM if undiagnosed before pregnancy and health care services not accessed until after 20 weeks of gestation. The delivery of prenatal outreach services provided in rural and remote communities and within FN communities in Manitoba limits this possibility. Third, treaty status was used to identify FN heritage; thus, FN people who, for historical reasons, were not assigned treaty status could have been incorrectly classified as non-FN. Misclassification of FN women as non-FN would, if anything, lessen the differences found between the groups. Finally, the study was conducted in one province in Canada, which may limit generalizability to other populations. However, we believe that the results are generalizable to other populations within a publically funded health care system because of the rigor applied to definitions and the large, population-based study design.

In conclusion, exposure to GDM in utero and FN status are both associated with an increased risk for type 2 diabetes in offspring in the first 30 years of life. FN status did not modify the risk of type 2 diabetes after exposure to GDM; however, FN status had a stronger impact on the development of type 2 diabetes in offspring than GDM. This study highlights that GDM in both FN and non-FN women is an important modifiable risk factor and that prevention of GDM could reduce the prevalence of subsequent type 2 diabetes in offspring. Interrupting the vicious cycle of in utero exposure to diabetes is crucial to improve the health of subsequent generations. This study adds unique and rigorous evidence to the global public health debate about the impact of GDM on the long-term health of offspring.

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