

Association of Gestational Diabetes and Type 2 Diabetes Exposure In Utero With the Development of Type 2 Diabetes in First Nations and Non-First Nations Offspring

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 Supplemental content

IMPORTANCE Type 2 diabetes is increasing worldwide, disproportionately affecting First Nations (FN) people. Identifying early-life determinants of type 2 diabetes is important to address the intergenerational burden of illness.

OBJECTIVE To investigate the association of in utero exposure to gestational diabetes and type 2 diabetes, stratified by FN status, with the development of type 2 diabetes in offspring.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was derived from the linkage of a pediatric diabetes clinical database and a population-based research data repository in Manitoba, Canada. Mother-infant dyads with a hospital birth or midwifery report in the data repository between April 1, 1984, and April 1, 2008, were identified. The dates of analysis were August through December 2017. Children identified with type 1 diabetes, monogenic diabetes, or secondary diabetes were excluded.

EXPOSURES Primary exposures included maternal gestational diabetes or type 2 diabetes and FN status.

MAIN OUTCOMES AND MEASURES The primary outcome was incident type 2 diabetes in offspring by age 30 years.

RESULTS In this cohort study of 467 850 offspring (mean follow-up, 17.7 years; 51.2% male), FN status and diabetes exposure were associated with incident type 2 diabetes in offspring after adjustment for sex, maternal age, socioeconomic status, birth size, and gestational age. Type 2 diabetes exposure conferred a greater risk to offspring compared with gestational diabetes exposure (3.19 vs 0.80 cases per 1000 person-years, $P < .001$). Compared with no diabetes exposure, any diabetes exposure accelerated the time to the development of type 2 diabetes in offspring by a factor of 0.74 (95% CI, 0.62-0.90) for gestational diabetes and a factor of 0.50 (95% CI, 0.45-0.57) for type 2 diabetes. First Nations offspring had a higher risk compared with non-FN offspring (0.96 vs 0.14 cases per 1000 person-years, $P < .001$). First Nations offspring had accelerated type 2 diabetes onset by a factor of 0.52 (95% CI, 0.49-0.55) compared with non-FN offspring. Neither interaction between FN and type 2 diabetes (0.92; 95% CI, 0.80-1.05) nor interaction between FN and gestational diabetes (0.97; 95% CI, 0.77-1.20) was significant ($P = .21$ and $P = .75$, respectively).

CONCLUSIONS AND RELEVANCE Important differences exist in offspring risk based on type of diabetes exposure in utero. These findings have implications for future research and clinical practice guidelines, including early pregnancy screening and follow-up of the offspring.

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The developmental theory of health and disease posits that exposures in early life preprogram offspring to develop chronic disease by associations with developmental pathways.¹ Maternal nutrition, gestational weight gain, and diabetes status in pregnancy are risk factors for childhood obesity and its complications.²⁻⁵ Rates of maternal diabetes in pregnancy have increased over the last 20 years, in part being driven by the increasing rates of childhood type 2 diabetes. Researchers among the Pima Indian population, which included a mix of type 2 diabetes and gestational diabetes exposure, reported an increased risk for type 2 diabetes and obesity in offspring.⁶ The SEARCH study⁷ supported these observations, revealing that maternal diabetes and obesity exposure attributed to 47% of type 2 diabetes risk to offspring. In a small case-control study,⁴ exposure to maternal type 2 diabetes was associated with a 14-fold increased risk of childhood type 2 diabetes, while gestational diabetes exposure was associated with a 4-fold increased risk.

Understanding the burden of risk to offspring with exposure to maternal gestational diabetes or type 2 diabetes has significant implications for the standard screening and care of pregnant women. Current Diabetes Canada⁸ guidelines recommend diabetes screening after the first trimester. Recently, the American Diabetes Association⁹ has addressed potential differences between gestational diabetes and type 2 diabetes in pregnancy and recommends earlier screening (at 4-12 weeks), despite a lack of evidence for this recommendation.

Type 2 diabetes prevalence has increased, and worldwide indigenous people are disproportionately affected, including First Nations (FN) people of Canada.¹⁰ Many affected Canadian children reside in Manitoba,¹¹ where FN people comprise 60% of the indigenous population (14% of the total Manitoba population), with 70% living in rural or remote communities.¹² In 2010 to 2011, the annual incidence of childhood-onset type 2 diabetes was 25 cases per 100 000 children in Manitoba, which is 20-fold higher than in other provinces.¹³ Approximately 90% of children in Manitoba living with type 2 diabetes have FN status.¹³ Colonization, dislocation, forced relocation, historical trauma, geographical isolation, food security, and poverty are important factors when considering these trends.

Type 2 diabetes is associated with poverty and lower socioeconomic status, yet it is not often documented as a traditional risk factor; the intergenerational nature of type 2 diabetes among FN people is unquestionably related to historical trauma and loss of language, culture, and land associated with colonization.¹⁴⁻¹⁶ In utero exposure to stress and adversity likely has associations in future generations by preprogramming poor health outcomes.¹⁷ An improved understanding of all early-life exposures that lead to the increasing incidence of type 2 diabetes in childhood is essential to improve the health of at-risk children worldwide.

Our study objective was to address knowledge gaps regarding risk to offspring with gestational diabetes and type 2 diabetes exposure. We constructed a cohort of FN offspring and non-FN offspring exposed to maternal gestational diabetes, type 2 diabetes, or no diabetes to investigate the association

Key Points

Question Do children and young adults exposed in utero to gestational diabetes or type 2 diabetes have the same risk of developing type 2 diabetes?

Findings In this cohort study of 467 850 offspring, First Nations status and type 2 diabetes exposure were associated with the highest rates of type 2 diabetes in offspring. Rates of type 2 diabetes were significantly different for gestational diabetes and type 2 diabetes exposures.

Meaning Gestational diabetes and type 2 diabetes exposures confer significantly different risk to offspring, suggesting benefits of earlier screening in pregnancy and differential follow-up of the offspring.

of different diabetes exposures with the development of early-onset (up to age 30 years) type 2 diabetes. We hypothesized that FN women and their offspring would disproportionately have diabetes and that type 2 diabetes would be a significantly higher-risk exposure to offspring compared with gestational diabetes.

Methods

Data for this study were derived from the Diabetes Education Resource for Children and Adolescents (DERCA) clinical database, which contains clinical and biochemical information on all patients participating in the pediatric diabetes program in Manitoba. DERCA is the only pediatric diabetes referral center serving the Manitoba population. In our study among youth (age range, 0-18 years) with type 2 diabetes, approximately 60% of cases were identified in DERCA.

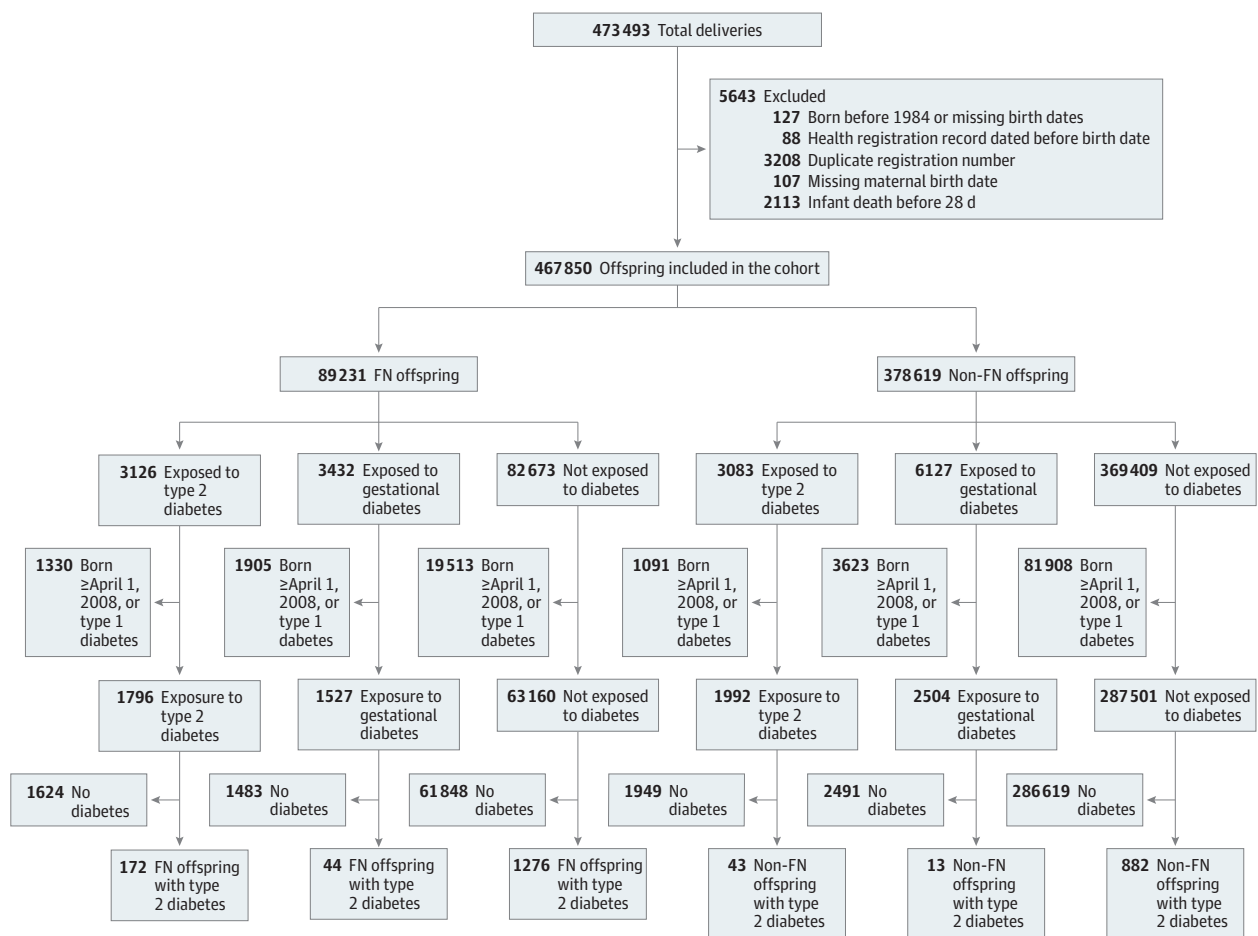
The DERCA clinical database was linked through an encrypted personal health number to the population-based Manitoba Population Research Data Repository (hereafter referred to as the Repository).¹⁸ *International Classification of Diseases, Ninth Revision (ICD-9)* and *Tenth Revision (ICD-10)* codes were used to search physician billing, hospital discharge abstracts, medical services, and midwifery reports (2000 to 2015) to identify women diagnosed as having gestational diabetes and type 2 diabetes using previously developed codes.¹⁹ In 1970, Manitoba prenatal and obstetrical records were combined and collected for all hospital births (hospital births comprise 99% of provincial births),¹⁸ and these data were incorporated into the Repository. Midwifery reports were added to the Repository in 2000.

Ethics approval was granted by the Human Research Ethics Board at the University of Manitoba, the Manitoba Health Information Privacy Committee, and the Manitoba First Nations Health Information Governance Committee. Individual informed consent was not obtained for this study because the data were analyzed from a large population database of deidentified health records.

Study Population

All mother-infant dyads with a hospital birth or midwifery report in the Repository between April 1, 1984, and April 1, 2008,

Figure 1. Inclusion and Exclusion for the Full Cohort



FN indicates First Nations.

were identified (Figure 1). Mothers and children identified in the DERCA clinical database as having type 1 diabetes, monogenic diabetes, or secondary diabetes were excluded, as were children born after April 1, 2008, because they would be aged 7 years or younger at the last follow-up. The dates of analysis were August through December 2017.

Primary Outcome of Incident Type 2 Diabetes in Offspring by Age 30 Years

A diagnosis of incident diabetes in offspring in the first 30 years of life was defined as 1 hospitalization or 2 physician visits within a 2-year period with a diagnosis of diabetes (ICD-9 or ICD-10), or it was identified by a diagnosis of type 2 diabetes in the DERCA clinical database. Offspring who were born in Manitoba before April 1, 2008, but moved out of the province before the study end date were included in the study until they left Manitoba, which was a censoring event for follow-up. Follow-up of the offspring ended on April 1, 2015.

Primary Exposures

Maternal Gestational Diabetes or Type 2 Diabetes

All pregnant women between 1981 and 2011 with a diagnosis of either gestational diabetes or type 2 diabetes who were

Manitoba residents with live offspring were identified. Gestational diabetes was defined as incident diabetes diagnosis between 21 weeks' gestation and 6 weeks' postpartum. Maternal type 2 diabetes was defined by a diabetes diagnosis in at least 1 hospital discharge or 2 outpatient physician diagnoses within the 3 years before 21 weeks' gestation.

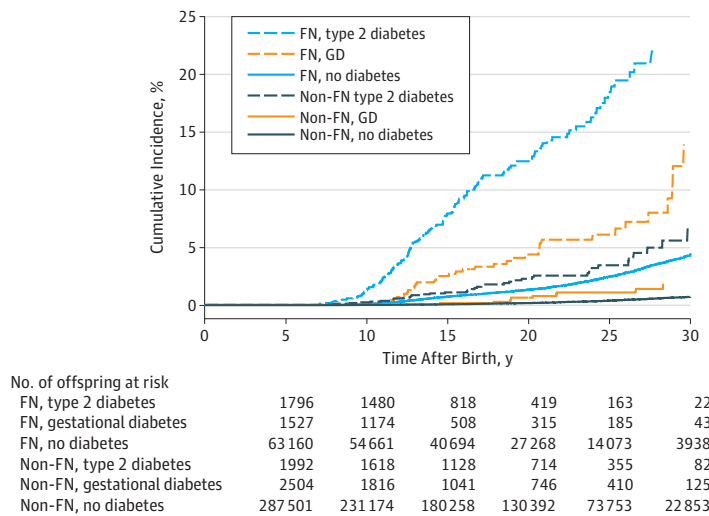
FN Status

First Nations status was determined by using the FN identifier. Permission was obtained 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.

Covariates

Birthweight, gestational age, sex, a Socioeconomic Factor Index (SEFI), urban region of residence, and birth year were included as potential confounders of the association between diabetes exposure and type 2 diabetes in offspring. Birthweight was categorized as large for gestational age (LGA) or small for gestational age (SGA) based on the lambda-mu-sigma method to calculate z scores.²⁰ Cutoffs for LGA and SGA were greater than 90% and less than 10%, respectively. Preterm birth was defined as a live birth

Figure 2. Kaplan-Meier Survival Curves of the Cumulative Incidence of Type 2 Diabetes in Offspring by First Nations (FN) Status and In Utero Diabetes Exposure



before 37 weeks' gestation. Urban vs rural region of residence was defined using a postal code conversion file for the province of Manitoba. Socioeconomic status was determined using the previously described SEFI, which applies area-level measures based on income, education, employment, and family structure.²¹ Maternal weight was captured from the hospital abstracts and used for a subanalysis of the cohort.

Statistical Analysis

Baseline characteristics are reported as means or medians (ranges) for continuous characteristics and as percentages for categorical characteristics. χ^2 Tests and analyses of variance were performed to investigate differences between exposure groups. Kaplan-Meier curves (Figure 2) were used to estimate the cumulative incidence rate for the development of type 2 diabetes in offspring. Analyses of Schoenfeld²² residuals indicated violation of the proportional hazards assumption required for Cox proportional hazards regression models. Therefore, we fitted accelerated failure time (AFT) models. We considered log-normal, log-logistic, exponential, Weibull,²³ and gamma distributions, with the gamma distribution providing the best fit as assessed by the Akaike information criterion. In AFT models, the exponentiated regression coefficients correspond to acceleration factors. Therefore, an antilogarithm for the regression coefficient of 1.0 shows no association with the time to the development of type 2 diabetes in offspring, with values less than 1.0 indicating a decrease in the time to event (offspring develop type 2 diabetes at a younger age) and values greater than 1.0 indicating a delay in the development (1.0 is the null value). An unadjusted model was fitted with exposure to diabetes and FN status. Adjustment covariates were chosen a priori based on previous literature.^{1,2,4,6,24} We included covariates in a stepwise manner. We also included interaction between FN status and exposure to diabetes, interaction between FN status and the SEFI, and interaction between FN status and region of residence. Although interactions between FN status and type 2 diabetes and gestational diabetes exposure

were not significant, they were interactions of interest that improved model fit and were retained. All other covariates and interactions improved model fit and were retained. A sensitivity analysis was performed to investigate the association of unmeasured confounders.²⁵

Data analysis was completed using statistical software (SAS, version 9.4; SAS Institute Inc). Kaplan-Meier curves were created using R (version 3.3.0; <https://cran.r-project.org/>) with ggplot2 (version 2.2.1; <https://cran.r-project.org/web/packages/ggplot2/index.html>). Two-sided *P* values were used.

Results

In total, 473 493 deliveries were identified from the Repository between 1984 and 2008. After removing offspring with missing or presumed erroneous data, the cohort consisted of 89 231 FN offspring and 378 619 non-FN offspring. In the final cohort of 467 850 offspring, the mean follow-up was 17.7 years, and 51.2% were male.

Overall, 2.0% of pregnancies were complicated by gestational diabetes, and 1.3% of pregnancies were complicated by type 2 diabetes. First Nations mothers had the highest burden of diabetes complicating pregnancy. In total, 3432 FN offspring and 6127 non-FN offspring were exposed to gestational diabetes, and 3126 FN offspring and 3083 non-FN offspring were exposed to type 2 diabetes (Figure 1). After excluding offspring born after April 1, 2008, and offspring diagnosed as having diabetes other than type 2 diabetes, the remaining cohort consisted of 358 480 offspring, with 2430 (0.7%) developing type 2 diabetes before age 30 years.

Offspring Characteristics, Stratified by FN Status and Diabetes Exposure

Compared with offspring exposed in utero to gestational diabetes, offspring exposed in utero to type 2 diabetes were more likely

Table 1. Descriptive Statistics of 358 480 Offspring in the Cohort Born Between 1984 and 2008 for First Nations (FN) vs Non-FN Mother-Infant Dyads^a

Variable	FN			P Value	Non-FN			P Value
	Type 2 Diabetes	Gestational Diabetes	No Diabetes		Type 2 Diabetes	Gestational Diabetes	No Diabetes	
No.	1796	1527	63 160	NA	1992	2504	287 501	NA
Birthweight, mean (SD), kg	3.5 (0.7)	3.7 (0.6)	3.5 (0.6)	<.001	3.4 (0.7)	3.5 (0.6)	3.4 (0.6)	<.001
LGA, %	38.4	36.7	12.5	<.001	29.8	19.1	7.4	<.001
SGA, %	4.2	2.6	7.1	<.001	5.4	5.7	8.7	<.001
Preterm birth, %	27.7	13.2	6.7	<.001	23.7	10.1	5.9	<.001
Female, %	47.8	47.2	49.2	.17	49.3	46.4	48.7	.06
SEFI, %								
Low (>1)	69.5	70.5	66.9		13.2	10.2	9.5	
Low to middle (>0 to ≤1)	22.9	20.9	22.0	<.001	34.3	34.4	33.4	<.001
Middle (-1 to ≤0)	6.6	7.0	9.2		39.5	42.0	40.6	
High (less than -1)	1.1	1.6	1.9		13.0	13.4	16.5	
Urban region of residence, %	25.4	21.4	31.6	<.001	66.1	64.7	63.1	.007
Birth year, %								
1984-1988	5.7	9.4	16.8		12.8	14.5	22.6	
1989-1993	13.5	9.6	21.7		19.1	15.8	23.3	
1994-1998	19.4	10.4	21.4	<.001	22.3	14.2	20.6	<.001
1999-2003	27.7	12.2	21.3		22.1	12.6	18.2	
2004-2008	33.7	58.4	18.8		23.7	42.9	15.3	
Follow-up time, median (Q1, Q3), y	13.5 (9.6, 18.9)	10.3 (8.6, 17.3)	17.6 (11.8, 23.3)	<.001	15.5 (10.1, 21.8)	11.0 (8.4, 20.8)	17.8 (10.8, 24.0)	<.001

Abbreviations: NA, not applicable; SEFI, Socioeconomic Factor Index; LGA, large for gestational age; SGA, small for gestational age.

^a Birth years are defined from January 1 to December 31. The 1984 data start on April 1, and the 2008 data end on March 31. χ^2 Tests were performed for

categorical variables, analyses of variance were performed for continuous variables represented with a mean (birth weight and SEFI), and Wilcoxon rank sum tests were performed for continuous variables represented with a median (follow-up time).

to be LGA (FN and non-FN) or SGA (FN only) (Table 1). Both gestational diabetes exposure and type 2 diabetes exposure in utero were associated with increased prematurity, with significantly higher rates for type 2 diabetes compared with gestational diabetes. No sex differences were observed in offspring between groups. First Nations mother-infant dyads lived in neighborhoods of significantly lower socioeconomic status compared with non-FN dyads. The highest rates of maternal gestational diabetes and type 2 diabetes were in the lowest socioeconomic neighborhoods. A lower proportion of FN offspring were living in urban centers compared with non-FN offspring. Within FN dyads, living in urban centers was associated with lower gestational diabetes and type 2 diabetes exposure in utero, whereas the opposite association was found for non-FN dyads.

Kaplan-Meier Survival Curves of the Cumulative Incidence of Type 2 Diabetes in Offspring by Exposure Group

The cumulative incidence of type 2 diabetes in offspring was the highest in offspring born to FN mothers with type 2 diabetes in pregnancy (5.6 cases per 1000 person-years), while the lowest incidence was in non-FN offspring not exposed to gestational diabetes or type 2 diabetes (0.1 case per 1000 person-years) (Table 2, Figure 1). Overall, FN offspring had a higher incidence of type 2

diabetes compared with non-FN offspring. First Nations offspring who were unexposed to diabetes had similar rates as non-FN offspring who were exposed to type 2 diabetes. Type 2 diabetes exposure conferred a greater risk to offspring compared with gestational diabetes exposure (3.19 vs 0.80 cases per 1000 person-years, $P < .001$) (Table 2).

Survival Models

The parametric survival models of the full cohort describe the association of each exposure variable with the time to the development of type 2 diabetes in offspring (Table 2). Both gestational diabetes exposure and type 2 diabetes exposure were associated with accelerated time to the development of type 2 diabetes in offspring but with significantly different associations. Gestational diabetes exposure shortened the time to the development of type 2 diabetes in offspring by a factor of 0.74 (95% CI, 0.62-0.90) compared with type 2 diabetes exposure, which shortened the time to the development of type 2 diabetes by a factor of 0.50 (95% CI, 0.45-0.57). First Nations offspring developed type 2 diabetes earlier by a factor of 0.52 (95% CI, 0.49-0.55) compared with non-FN offspring. Each 1 SD increase in the SEFI, representing increased deprivation, was associated with a decrease in the time to the development of type 2 diabetes by 8.0%. The variables

Table 2. Crude Incidence Rates and Accelerated Failure Time (AFT) Survival Model With γ Distribution for the Full Cohort and Subset With Maternal Weights^a

Variable	Incidence Rate per 1000 Person-Years			AFT Exponential Estimate (95% CI)	
	Type 2 Diabetes	Gestational Diabetes	No Diabetes	Type 2 Diabetes vs No Diabetes	Gestational Diabetes vs No Diabetes
Full Cohort (N = 356 431)					
All	3.19	0.80	0.26	0.47 (0.44-0.51)	0.72 (0.65-0.61)
FN	5.63	1.67	0.83	0.24 (0.17-0.33)	0.37 (0.23-0.59)
Non-FN	1.17	0.29	0.13	0.50 (0.45-0.57)	0.74 (0.62-0.90)
Subset With Maternal Weights (n = 90 296)					
All	2.69	NA	0.15	0.48 (0.40-0.56)	NA

Abbreviations: FN, First Nations; NA, not applicable.

^a The AFT Exp estimates were adjusted for sex, maternal age, socioeconomic status, birth size, and gestational age. The model interactions included interaction between FN status and the Socioeconomic Factor Index (SEFI), interaction between FN status and region of residence, and interactions between FN status and type 2 diabetes and gestational diabetes.

LGA, SGA, preterm birth, and female sex were all associated with a shorter time to the development of type 2 diabetes in offspring (eTable 1 in the Supplement).

Maternal Weight Subanalysis

Maternal weight between 15 and 20 weeks' gestation was available for 90 296 offspring (Table 2). This subanalysis was restricted to a comparison between exposure to type 2 diabetes and no diabetes exposure because of small numbers. The median maternal weight was significantly different between the 2 groups, with 78.0 kg (95% CI, 66.2-93.4) for women who had type 2 diabetes in pregnancy vs 66.7 kg (95% CI, 59.9-77.0) for women who did not have diabetes in pregnancy. The proportions of offspring born LGA, SGA, and preterm and with a lower mean SEFI were significantly different between offspring exposed to type 2 diabetes compared with those with no diabetes exposure (eTable 2 in the Supplement). The parametric survival model showed a similar association of type 2 diabetes exposure compared with no diabetes, shortening the time to the development of type 2 diabetes in offspring by a factor of 0.48 (95% CI, 0.40-0.56). A smaller association of maternal weight was seen with each 1-kg increase in weight, reducing the time to the development of type 2 diabetes in offspring by a factor of 0.99 (95% CI, 0.99-1.00). The overall shape and association between groups in the Kaplan-Meier survival curves did not change substantially from the survival curves of the full cohort (eFigure in the Supplement).

Discussion

This population-based historical prospective cohort study investigated the unique risks of gestational diabetes and type 2 diabetes exposure to offspring born to FN and non-FN mothers. Overall, 2.0% of pregnancies were complicated by gestational diabetes, and 1.3% of pregnancies were complicated by type 2 diabetes. Our results confirm that diabetes in pregnancy is an important risk factor for the development of type 2 diabetes in offspring, with type 2 diabetes exposure having the greatest associated risk. The pregnancies of FN women were more often complicated by gestational diabetes (3.8%) and type 2 diabetes (3.5%) compared with the pregnancies of non-FN women (1.6% and 0.8%, respectively) (Figure 1 and Table 1). Gestational diabetes and type 2 diabetes exposure had a similar association with the time to the development of type 2 diabetes in both FN and non-FN offspring, suggesting that early

identification and determination of gestational diabetes or type 2 diabetes in pregnancy is important irrespective of ethnicity.

Exposure to type 2 diabetes in utero reduced the time to the development of youth-onset type 2 diabetes. The mechanisms underlying the predilection for earlier diagnosis is unclear; however, it is likely due to prenatal programming involving altered β cell mass or function and abnormal lipid metabolism. Previous evidence has shown that exposure to any maternal diabetes resulted in a younger age at onset of type 2 diabetes in offspring.²⁶ Exposure to isolated gestational diabetes has previously shown an increase in risk of the development of type 2 diabetes in offspring (hazard ratio, 3.03).²⁴ In that study, FN status also had a strong association with the development of type 2 diabetes in offspring (hazard ratio, 4.86). Our study supports an independent association between FN status and gestational diabetes and extends these findings by reporting the stronger association of childhood type 2 diabetes in offspring exposed to type 2 diabetes compared with gestational diabetes.

The present study is consistent with the previous descriptions of female predominance of early-onset type 2 diabetes.²⁷ The reasons for this predominance remain unclear but may be due to a different body habitus compared with that of young men. Socioeconomic factors were associated with the time to type 2 diabetes in offspring only among non-FN individuals. However, approximately 70% of FN mothers lived in the lowest socioeconomic areas, likely reducing the association of the SEFI (socioeconomic status) with the time to development of type 2 diabetes within the FN offspring.

Strengths and Limitations

Strengths of our study include the ability to link population-based data to a clinical registry, which allowed separation of gestational diabetes exposure from type 2 diabetes exposure and classification of offspring diabetes type, which has been a limitation in other population-based administrative studies. In addition, we used validated algorithms to define type of diabetes exposure in pregnancy and offspring type 2 diabetes diagnosis. We also used validated composite measures of socioeconomic factors that expand on traditional income quintiles to include educational attainment, single-parent homes, and housing.

Limitations to our study include the potential association of unmeasured confounders with our findings, including absence of glycated hemoglobin levels and offspring anthropometrics. In addition, maternal weight data were limited, and maternal body mass index was unavailable. A sensitivity analysis (eTable

3 in the Supplement) suggests that our findings are robust to potential unmeasured confounders. However, there is potential for misclassification of offspring diabetes type. The DERCA clinical database has a capture rate of 87% for all pediatric diabetes²⁸ and greater than 99% for type 1 diabetes.²⁹ First Nations status was determined by registration in the National Indian Registry System, which excludes Métis and non-FN status individuals, who represent up to 30% of individuals with FN heritage.

Conclusions

Our study finds important risk differences to offspring based on diabetes exposure in utero. The highest rates of type 2 diabetes were observed in offspring born to FN mothers with type 2 dia-

betes. Inequities in income, educational opportunity, food security, and prenatal care sustain this health disparity to future generations. American Diabetes Association⁹ guidelines recommend preconception counseling, early screening, and aggressive glycemic management to mitigate risks to the mother and newborn. Our study establishes the importance of determining diabetes type early in pregnancy, with implications for offspring health. The data herein do not imply that FN status is a measure of intrinsic susceptibility but rather is a proxy for political and historical factors that contribute to the population risk. Addressing structural inequality and poverty at a policy level may contribute the most to reducing rates of diabetes in FN people. Our findings also inform practitioners of the need for routine early screening and diagnosis of type 2 diabetes in mothers and their offspring.

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Acquisition, analysis, or interpretation of data: Wicklow, Sellers, Sharma, Kroeker, Nickel, Shen. **Drafting of the manuscript:** Wicklow, Sharma, Nickel.

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