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Long-term Neurobehavioral and Metabolic Outcomes in Offspring of Mothers With Diabetes During Pregnancy: A Large, Population-Based Cohort Study in Ontario, Canada

Denice S. Feig, Azmina Artani, Ayesha Asaf, Ping Li, Gillian L. Booth, and Baiju R. Shah

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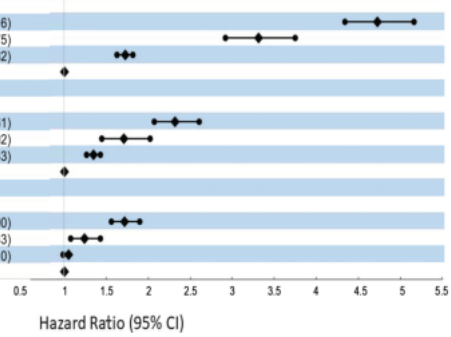
Long-Term Neurobehavioral and Metabolic Outcomes in Offspring of Mothers with Diabetes During Pregnancy: A large, population-based cohort study in Ontario, Canada.

Health Outcomes	NO.(%) of Mothers with Exposure	Adjusted Hazard Ratios (95% CI)
ADHD		
Type 1 diabetes	29,094 (0.85%)	1.43 (1.36-1.49)
Type 2 diabetes	19,745 (0.58%)	1.25 (1.17-1.34)
Gestational diabetes	172,817 (5.07%)	1.03 (1.01-1.06)
Unexposed	3,186,305 (93.45%)	
Autism		
Type 1 diabetes	29,094 (0.85%)	1.94 (1.80-2.09)
Type 2 diabetes	19,745 (0.58%)	1.64 (1.50-1.79)
Gestational diabetes	172,817 (5.07%)	1.40 (1.36-1.45)
Unexposed	3,186,305 (93.45%)	
Diabetes		
Type 1 diabetes	29,094 (0.85%)	4.73 (4.34-5.16)
Type 2 diabetes	19,745 (0.58%)	3.31 (2.92-3.75)
Gestational diabetes	172,817 (5.07%)	1.73 (1.63-1.82)
Unexposed	3,186,305 (93.45%)	
Hypertension		
Type 1 diabetes	29,094 (0.85%)	2.32 (2.07-2.61)
Type 2 diabetes	19,745 (0.58%)	1.71 (1.45-2.02)
Gestational diabetes	172,817 (5.07%)	1.35 (1.27-1.43)
Unexposed	3,186,305 (93.45%)	
Cardiovascular Disease		
Type 1 diabetes	29,094 (0.85%)	1.72 (1.56-1.90)
Type 2 diabetes	19,745 (0.58%)	1.24 (1.08-1.43)
Gestational diabetes	172,817 (5.07%)	1.05 (0.99-1.10)
Unexposed	3,186,305 (93.45%)	

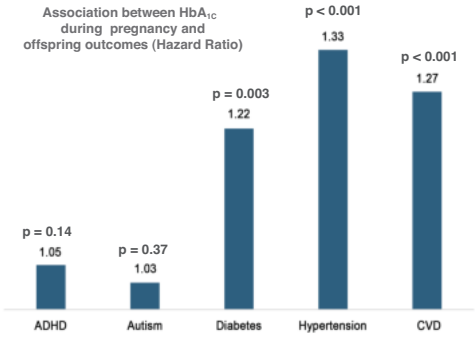


CVD, cardiovascular disease; DM, diabetes mellitus

Objectives:
- To determine if exposure to maternal diabetes is associated with adverse long-term outcomes in offspring, and if these outcomes are associated with maternal glycemia levels

Methods:
- Population-based cohort study of >3 million mother-infant pairs followed up to 29 years

Results:
- Exposure to maternal diabetes associated with increased risk of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, diabetes, hypertension and cardiovascular disease in offspring
- Gradient of risk by diabetes type
- In offspring of women with type 1 or 2 DM, glycemic levels associated with risk of cardio-metabolic outcomes but not neurobehavioral outcomes



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Offspring of women with diabetes are at increased risk of long-term chronic diseases, but there is scant evidence regarding the association between glycemia during pregnancy and these long-term outcomes.
- **What is the specific question(s) we wanted to answer?**
  Is there an association between pregnancy glycemic levels and the long-term risk of chronic diseases in offspring of mothers with diabetes?
- **What did we find?**
  Maternal diabetes was associated with neurobehavioral and cardiometabolic outcomes in offspring, with risk differences seen across diabetes subtypes. Maternal glycemic level during pregnancy was significantly associated with long-term cardiometabolic outcomes in offspring but not neurobehavioral outcomes.
- **What are the implications of our findings?**
  Maternal glycemic control during pregnancy provides a potentially modifiable risk factor to decrease cardiometabolic outcomes in offspring.

Long-term Neurobehavioral and Metabolic Outcomes in Offspring of Mothers With Diabetes During Pregnancy: A Large, Population-Based Cohort Study in Ontario, Canada

https://doi.org/10.2337/dc24-0108

Denice S. Feig,[1,2,3,4] Azmina Artani,[4] Ayesha Asaf,[4] Ping Li,[4] Gillian L. Booth,[1,4,5] and Baiju R. Shah[1,4,6]

ORIGINAL ARTICLE

OBJECTIVE

Offspring of women with diabetes are at increased risk of developing neurobehavioral and cardiometabolic disorders, but there is scant evidence regarding the association between glycemic level during pregnancy and these long-term offspring outcomes.

RESEARCH DESIGN AND METHODS

We conducted a population-based, cohort study of deliveries in Ontario between April 1991 and March 2018. Women had preexisting diabetes, gestational diabetes, or no diabetes. We applied a Cox proportional hazard model to examine the risk of developing attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and cardiometabolic outcomes in offspring and assessed the association between pregnancy HbA_{1c} levels and risk of outcomes, adjusting for confounders.

RESULTS

A total of 3,407,961 mother/infant pairs were followed up to 29 years. Using a Cox proportional hazard model, offspring of women with type 1 diabetes had the highest risk of ADHD (adjusted hazard ratio [aHR] 1.43 [95% CI 1.36–1.49]), ASD (aHR 1.94 [1.80–2.09]), diabetes (aHR 4.73 [4.34–5.16]), hypertension (aHR 2.32 [2.07–2.61]), and cardiovascular disease (CVD) (aHR 1.72 [1.56–1.90]), followed by offspring of women with type 2 diabetes and gestational diabetes compared with those unexposed. Among women with preexisting diabetes, there was an association between level of pregnancy HbA_{1c} and offspring diabetes (aHR 1.22 [95% CI 1.12–1.32]), hypertension (aHR 1.42 [1.29–1.57]), and CVD (aHR 1.20 [1.11–1.29]) but no statistically significant association with neurobehavioral outcomes.

CONCLUSIONS

In utero exposure to maternal diabetes was associated with an increase in ADHD, ASD, and cardiometabolic outcomes in offspring, with differences seen across diabetes subtypes. Pregnancy glycemia was associated with cardiometabolic outcomes, but not neurobehavioral outcomes, and provides a potentially modifiable risk factor to decrease cardiometabolic outcomes in offspring.

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[2]Sinai Health System, Mount Sinai Hospital, Toronto, Ontario, Canada
[3]Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada
[4]Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada
[5]Department of Medicine, St. Michael's Hospital, Unity Health, Toronto, Ontario, Canada
[6]Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Corresponding author: Denice Feig, d.feig@utoronto.ca

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The incidence of diabetes in pregnancy has risen dramatically over the last decades (1). In a population-based cohort study from Alberta, Canada, performed between 2005 and 2018, the rate of gestational diabetes mellitus (GDM) more than doubled, from 42.3 to 101.8 per 1,000 deliveries, as did the rate of type 2 diabetes in pregnancy, from 2.6 to 6.4 per 1,000 deliveries, while the rate of type 1 diabetes in pregnancy remained steady at 3.0 per 1,000 deliveries per year (2). Women with diabetes in pregnancy have high rates of adverse pregnancy outcomes, such as preeclampsia, preterm birth, and cesarean sections, while their infants have increased rates of macrosomia, respiratory distress, congenital anomalies, neonatal hypoglycemia, and neonatal intensive care unit admissions (3,4). There is also increasing evidence that offspring of women with diabetes are at risk for developing long-term complications. These include obesity, dysglycemia, and cardiovascular (CV) disorders (5), as well as neurobehavioral disorders such as cognitive deficiency, behavioral disorders, and autism spectrum disorder (ASD) (6). While there is much evidence that hyperglycemia is associated with these short-term birth outcomes (7), there is still scant evidence that blood glucose levels during pregnancy are associated with these long-term offspring outcomes. If this were the case, then this would provide a potentially modifiable risk factor that could reduce these long-term adverse outcomes.

The aim of this study was to determine whether offspring of women with preexisting type 1 and 2 diabetes and GDM, followed up to adolescence and young adulthood, are at increased risk of developing adverse neurodevelopmental and metabolic outcomes and assess whether a potentially modifiable risk factor, such as blood glucose levels during pregnancy, is associated with these long-term outcomes.

RESEARCH DESIGN AND METHODS

Study Design and Population

We conducted a population-based, retrospective cohort study that included all mothers delivering in Ontario between 1 April 1991 and 31 March 2018 aged 16 to 55 years and their live newborns. Offspring were followed up to 31 March 2020 (i.e., 2–29 years).

In Ontario, health care is universally available to all residents under a single-payer system, and within this system, all health care visits and hospitalizations are recorded. We used health administrative databases available in Ontario, including the provincial health insurance registry, physician billing claims, the Canadian Institute for Health Information Discharge Abstract Database, a data set linking inpatient records of delivering mothers and their newborns (MOMBABY), the National Ambulatory Care Reporting System for emergency department visits, and the Ontario Mental Health Reporting System (Supplementary Table 1). We used the Ontario Laboratories Information System (OLIS), a repository of laboratory results from community and hospital laboratories for the HbA_{1c} results. OLIS captures a subset of laboratory results done in the province. These data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data for health system evaluation and improvement.

We excluded mother and newborn pairs who did not have a valid provincial health card number and had missing age or sex information. We excluded from the final study cohort pairs with birth date and delivery admission date >150 days apart and newborns with birth weight ≤ 400 g. The birth date of the baby was the cohort index date (Supplementary Table 2*A* and *B*).

Exposure

We identified mothers who had preexisting type 1 and type 2 diabetes before pregnancy and those who developed GDM during the pregnancy using validated algorithms for preexisting diabetes, type 1, and GDM (8–10) (Supplementary Table 3). Those mothers who had preexisting diabetes but did not satisfy the type 1 diabetes algorithm were considered to have type 2 diabetes. Mothers who did not meet the case definition for any type of diabetes were used as a comparison group.

Maternal glycemia was assessed in women with preexisting diabetes and defined by an HbA_{1c} taken during pregnancy closest to the delivery date.

Outcomes

Neurobehavioral conditions included attention deficit hyperactivity disorder (ADHD) and ASDs. Cardiometabolic conditions included diabetes, hypertension, and CV disorders. These outcomes were ascertained using validated algorithms and *International Classification of Diseases*-9th Revision/ICD-10 diagnosis codes listed in Supplementary Table 3. CV disorders were a composite of diagnoses, including acute myocardial infarction, acute coronary syndrome, congestive heart failure, or cardiac arrhythmia (Supplementary Table 3). We assessed the risk of these outcomes among offspring of mothers having preexisting diabetes, GDM, and those with no diabetes. Among mothers with preexisting diabetes, we further examined the conditions among mothers with type 1 and type 2 diabetes.

Covariates

We obtained sociodemographic information for mothers and infants in our cohort using the Registered Persons Database, including age of the mother at delivery, sex of the infant, and postal code of their residence. The postal code was then linked to Statistics Canada's Postal Code Conversion File to identify neighborhood income quintiles and area of residence (rural vs. urban). We assessed maternal- and infant-related factors at the time of delivery, including multiple gestation, parity, neonatal hypoglycemia, and birth weight (Supplementary Table 3).

Statistical Analyses

We compared sociodemographic characteristics and maternal- and infant-related factors among mothers with preexisting or GDM with mothers who did not have diabetes by reporting the mean (SD) and median (interquartile range) for continuous variables and counts and proportions for categorical variables. Differences between groups were compared using standardized differences, where a value of ≥ 0.1 was considered important.

We applied a Cox proportional hazard model to examine the risk of developing ADHD, ASD, and cardiometabolic outcomes in infants of mothers with preexisting diabetes and GDM compared with mothers without diabetes in the follow-

up period. This model was applied to a further analysis that categorized preexisting diabetes into type 1 and type 2 diabetes. We present risk measures for the outcomes adjusted for maternal age, income quintile, rurality, parity, and multiple gestation at the time of delivery. We adjusted for preterm birth, neonatal hypoglycemia, and neonatal intensive care unit admission for a subset of infants in our cohort (data for these covariates was available from 1 April 2002 and onward). Models were hierarchical; therefore, they accounted for repeated measures of mothers who may have had multiple children during the study period. Offspring participants were censored when they reached the end of the study period or died during the study period without having experienced an outcome event.

The Cox proportional hazards model was applied when assessing the association between HbA_{1c} levels in mothers with preexisting diabetes and the risk of outcomes in their offspring. This analysis was completed on a subset of mothers with preexisting diabetes who had an available HbA_{1c} test between 1 April 2007 and 31 March 2018 (n = 14,911). This association was assessed in a continuous manner as well as a categorical one (i.e., $HbA_{1c} \leq 6.5\%$ or $>6.5\%$.

This project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*, and therefore, use of this data did not require a Research Ethics Board review.

Data and Resource Availability

The data set from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (e.g., health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS.

RESULTS

Of the 3,793,676 mother-infant pairs that delivered in Ontario between 1 April 1991 and 31 March 2018, we included 3,407,961 mother/infant pairs (Supplementary Table 2), comprising 48,839 with preexisting diabetes (29,094 offspring of mothers with type 1 diabetes, 19,745 offspring of women with type 2 diabetes), 172,817 offspring of women with GDM, and 3,186,305 offspring of mothers without diabetes (Table 1). Baseline characteristics are shown in Table 1. Women with preexisting diabetes and GDM tended to be older, more were in the lowest socioeconomic quintile, fewer lived in rural areas, and more were multiparous.

Offspring were followed for a median of 13.63 years, up to 29 years, with a total of >45 million person-years of follow-up. Offspring of women with type 1 diabetes had the highest frequency of ADHD, ASD, diabetes, hypertension, and CV disease (CVD) (see Supplementary Table 4 for absolute rates and Fig. 1 for cumulative incidence rates).

Using a Cox proportional hazard model, we determined the risk of these health outcomes according to maternal diabetes exposure, adjusted for age, parity, income quintile, multigestation, and rurality. There was a gradient of risk of ADHD across diabetes subtypes, from preexisting diabetes to GDM to no diabetes. After adjustment for age, parity, income quintile, multigestation, and rurality, the risk to offspring of women with preexisting diabetes notably increased (hazard ratio [HR] 1.36 [95% CI 1.32–1.41]), while the risk to offspring of women with GDM was minimally increased (HR 1.03 [1.01–1.06]) (Supplementary Table 5*A*). Further adjustment for preterm birth, small for gestational age, large for gestational age, or neonatal hypoglycemia did not materially change this estimate (Supplementary Table 6*A*). When the population was

Table 1—Characteristics of all included deliveries with preexisting diabetes, GDM, and those unexposed at the time of any birth between 1 April 1991 and 31 March 2018

Variable	Preexisting diabetes (n = 48,839)	GDM (n = 172,817)	Unexposed (n = 3,186,305)	Standardized difference*	Standardized difference**
Mother's age (years)					
Mean ± SD	32.37 ± 5.19	32.00 ± 5.23	29.57 ± 5.42	0.53	0.46
Median (IQR)	32 (29–36)	32 (29–36)	30 (26–33)	0.51	0.44
Baby's sex					
Female	23,805 (48.7)	82,989 (48.0)	1,554,092 (48.8)	0	0.02
Male	25,034 (51.3)	89,828 (52.0)	1,632,213 (51.2)	0	0.02
Income quintile					
1	12,874 (26.4)	45,820 (26.5)	712,159 (22.4)	0.09	0.1
2	9,686 (19.8)	37,146 (21.5)	639,458 (20.1)	0.01	0.04
3	9,911 (20.3)	35,062 (20.3)	639,927 (20.1)	0.01	0.01
4	9,610 (19.7)	31,697 (18.3)	646,682 (20.3)	0.02	0.05
5	6,484 (13.3)	22,025 (12.7)	529,579 (16.6)	0.09	0.11
Missing	274 (0.6)	1,067 (0.6)	18,500 (0.6)	0	0
Rural residence	3,634 (7.4)	11,451 (6.6)	309,791 (9.7)	0.08	0.11
Parity					
≥1	31,339 (64.2)	93,066 (53.9)	1,656,271 (52.0)	0.25	0.04
0	17,500 (35.8)	79,751 (46.1)	1,530,034 (48.0)	0.25	0.04
Multiple gestation	1,916 (3.9)	7,977 (4.6)	100,021 (3.1)	0.04	0.08

Data are presented as n (%) unless indicated otherwise. IQR, interquartile range. *Standardized difference between preexisting diabetes and unexposed to diabetes. **Standardized difference between GDM and unexposed to diabetes.

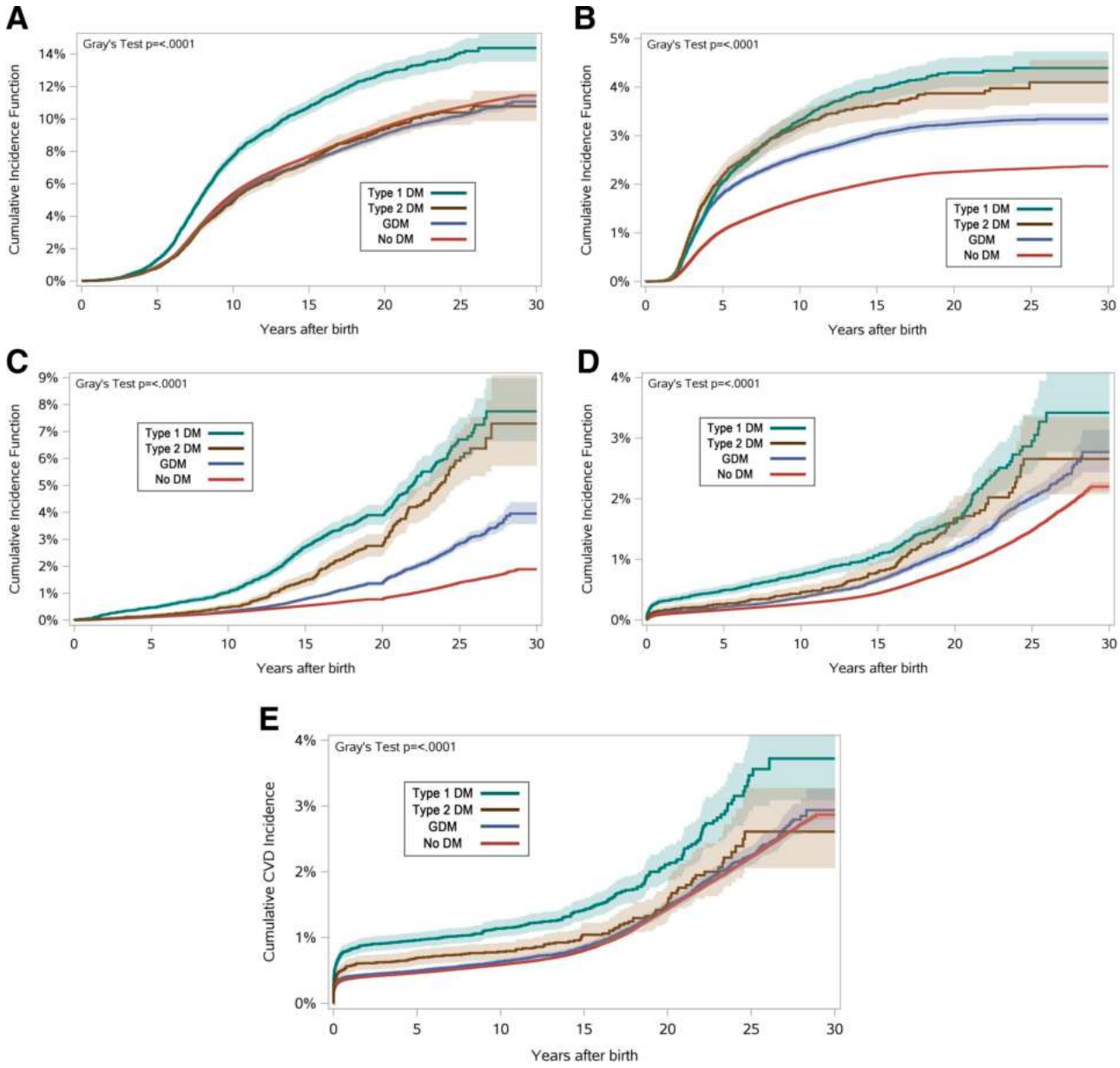

Figure 1—Cumulative incidence of ADHD (*A*), ASD (*B*), diabetes (dm) (*C*), hypertension (*D*), and CVD (*E*) in children born 1991–2018, by diabetes status of mothers at delivery. The shaded areas show the 95% CI.

categorized into types of preexisting diabetes, offspring of women with type 1 diabetes had the highest risk of ADHD, followed by a moderate risk in offspring of women with type 2 diabetes, and a minimally higher risk in offspring of women with GDM compared with unexposed offspring (Supplementary Table 7 and Fig. 2).

For ASD, we found a gradient in risk in offspring of women with diabetes, with the highest risk in women with preexisting diabetes (adjusted HR [aHR] 1.81 [95% CI 1.72–1.91]), followed by an increased risk seen in offspring of women with GDM (aHR 1.52 [1.48–1.57]) compared with those unexposed (Supplementary Table 5*B*). Further adjustment for preterm birth, small for gestational age, large for gestational age, or neonatal hypoglycemia did not materially change the estimate (Supplementary Table 6*B*). When we divided the cohort into women with type 1 diabetes, type 2 diabetes, and GDM, offspring of women with type 1 diabetes had the highest risk of ASD, followed by offspring of women with type 2 diabetes, followed by offspring of women with GDM, compared with unexposed offspring (Supplementary Table 7 and Fig. 2).

The risk for type 1 or type 2 diabetes in the offspring of women with diabetes was increased in women with preexisting diabetes (aHR 4.19 [95% CI 3.91–4.48]) and GDM (aHR 1.73 [1.64–1.83]) (Supplementary Table 5*C* and Supplementary Fig. 1). When divided by type of diabetes, the risk for diabetes in offspring was elevated in both women with type 1 diabetes (aHR 4.73 [4.34–5.16]), and type 2 diabetes (aHR 3.31 [2.92–3.75]) Supplementary Table 7 and Fig. 2).

The risk for hypertension was increased in offspring, with the highest risk in offspring of women with type 1 diabetes (aHR 2.32 [95% CI 42.07–2.61]), followed by offspring of women with type 2 diabetes (aHR 1.71 [1.45–2.02]), and

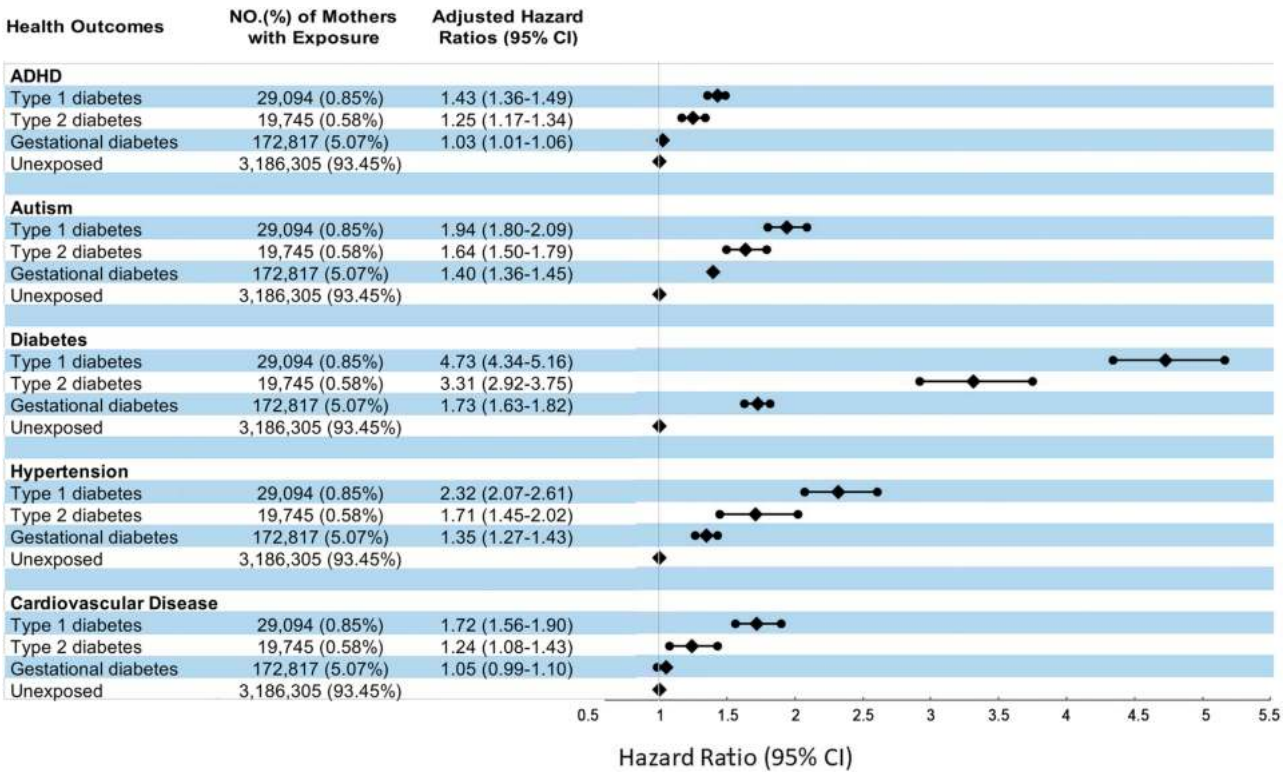

Figure 2—The risk of neurobehavioral and cardiometabolic outcomes in offspring of women with type 1 diabetes, type 2 diabetes, and GDM compared with those not exposed to diabetes in utero who delivered between 1 April 1991 and 31 March 2018.

increased as well in offspring of women with GDM (aHR 1.35 [1.27–1.43]) (Supplementary Table 7 and Fig. 2).

The risk for CVD was increased in offspring of women with type 1 disease (aHR 1.72 [95% CI 1.56–1.90]) and in offspring of women with type 2 diabetes (aHR 1.24 [1.08–1.43]) but did not reach significance in women with GDM (aHR 1.05 [0.99–1.10]) (Supplementary Tables 5*E* and 7 and Fig. 2).

We then evaluated the association between glycemia during pregnancy in women with preexisting diabetes and these long-term health outcomes in the offspring. A subset of women who delivered between 1 April 2007 and 31 March 2018 (n = 14,911) had an available HbA_{1c}. Laboratories in Ontario have incrementally joined the OLIS database, and therefore, some laboratories in the early years of the study were not yet contributing. However, characteristics of women who had HbA_{1c} levels available and those that did not have HbA_{1c} levels available (n = 13,779) were similar (Supplementary Table 8). In a Cox proportional hazards model adjusted for confounders, we did not find a statistically significant association between maternal glycemia and the neurobehavioral outcomes of ADHD and ASD. There was an association between offspring development of diabetes (aHR 1.24 [95% CI 1.12–1.37]), hypertension (aHR 1.31 [1.18–1.46]), and CVD (aHR 1.25 [1.14–1.36]) and the level of HbA_{1c}, closest to delivery (Table 2), with a higher risk in those with higher HbA_{1c} during pregnancy. We evaluated this association in a categorical fashion and found that those offspring whose mothers had an HbA_{1c} >6.5% (>48 mmol/mol) had a higher risk of these long-term cardiometabolic outcomes compared with those whose mothers had an HbA_{1c} of <6.5% (<48 mmol/mol) (Supplementary Table 9).

The proportion of individuals censored for loss of Ontario Health Insurance Plan coverage, as a proxy for out-migration, was low (5–7%), with fewer people with diabetes censored compared with those without diabetes (Supplementary Table 10).

CONCLUSIONS

In this large, population-based cohort study of offspring of women with diabetes monitored for up to 29 years, we found that in utero exposure to maternal diabetes was associated with an increase in several adverse long-term outcomes in the offspring, including neurodevelopmental and neurobehavioral outcomes, such as ADHD and ASD, as well as cardiometabolic outcomes such as diabetes, hypertension, and CVD. When divided into types of diabetes, there was a gradient of risk for these outcomes, with offspring of women with type 1 diabetes having the highest risk, followed by offspring of women with type 2 diabetes, and then offspring of women with GDM, who had a higher risk compared with offspring with no diabetes exposure in utero. In offspring of women with preexisting diabetes, glycemic level was strongly associated with cardiometabolic outcomes, such that the higher the HBA_{1c} of the mother during pregnancy, the higher the risk of these outcomes in their children. A statistically significant association with glycemia was not seen for the neurodevelopmental or neurobehavioral outcomes.

In this population-based study, we found a gradient of risk for ADHD in offspring of mothers with diabetes, according to diabetes type. Our findings are similar to those of Xiang et al. (11), who also found this gradient of risk. In their study, women with GDM requiring medication had a higher risk than the unexposed group, although women with GDM not requiring medication did not.

Table 2—The association between HbA_{1c} levels* and health outcomes in those with preexisting diabetes for deliveries between 1April 2007 and 31 March

Health outcome	Unadjusted HR (95% CI) (n = 14,918)	P value	Age-adjusted HR (95% CI) (n = 14,918)	P value	aHR** (95% CI) (n = 14,918)	P value
ADHD						
HbA_{1c} level	1.08 (1.01–1.16)	0.0293	1.05 (0.98–1.13)	0.1302	1.05 (0.98–1.13)	0.1409
ASD						
HbA_{1c} level	1.03 (0.96–1.11)	0.3769	1.04 (0.97–1.12)	0.2938	1.03 (0.96–1.11)	0.3741
Diabetes						
HbA_{1c} level	1.28 (1.16–1.40)	<0.0001	1.23 (1.12–1.36)	<0.0001	1.22 (1.09–1.35)	0.0003
Hypertension						
HbA_{1c} level	1.34 (1.19–1.51)	<0.0001	1.33 (1.18–1.49)	<0.0001	1.31 (1.17–1.47)	<0.0001
CVD						
HbA_{1c} level	1.29 (1.18–1.41)	<0.0001	1.27 (1.16–1.39)	<0.0001	1.25 (1.14–1.37)	<0.0001

*HbA_{1c} levels were taken during pregnancy closest to the delivery date and are meant to reflect maternal glycemic levels. **Adjusted for age, parity, income quintile, multigestation, rurality, and diabetes type.

Findings have been mixed in other studies. In a population-based study from Norway, ADHD was increased in offspring of women with type 1 but not type 2 diabetes, although number of women with type 2 diabetes was small (12). In a population-based study in Taiwan, there was an increased risk in children of mothers with type 2 diabetes but not type 1 diabetes and a mild increase in offspring of women with GDM (13); however, the number of women with diabetes in this study was considerably smaller than our study. Others have found an increased risk of ADHD in offspring of women with GDM if combined with low socioeconomic status (14,15). Studies in individuals with type 1 diabetes have shown that although the risk of ADHD in their offspring is higher in both mothers and fathers with type 1 diabetes, suggesting potentially an immune and/or genetic component, the risk was higher in offspring of mothers with type 1 diabetes compared with fathers with type 1 diabetes, suggesting a role for the in utero glycemic environment (16). Overall, the evidence suggests an increased risk of ADHD in mothers with diabetes, with a gradient according to types of diabetes.

In our study, offspring of women with all types of diabetes in pregnancy had an increased risk of ASD. We saw differences in risk ratios by diabetes subtype, with the highest risk in offspring of women with type 1 diabetes, followed by type 2 diabetes, and then GDM. This gradient of risk was seen in the study by Xiang et al. (17,18), where offspring of women with type 1 diabetes had the highest risk. Interestingly, they found an increased risk in offspring of women with GDM diagnosed before 26 weeks but not in those diagnosed after 26 weeks (17,18). This similarity suggests prolonged exposure to hyperglycemia leads to higher risk of ASD. Other evidence in the literature has been conflicting, with some studies finding an increased risk of ASD only in offspring of obese women with diabetes (19,20), others finding an increased risk, even after adjusting for maternal BMI (18,21,22), while others found no increase in risk of ASD in offspring of women with diabetes (23). A recent population-based study found an increased risk of ASD in offspring of women with type 2 diabetes and GDM but not in women with type 1 diabetes (13). Overall, given our findings, there does appear to be an increased risk of ASD in offspring of women with diabetes, with a gradient of risk seen.

The mechanism for this increased risk of ASD in offspring exposed to maternal diabetes is unknown. Potential factors associated with adverse effects on fetal brain development in offspring of mothers with diabetes include epigenetic changes, excessive inflammation, and oxidative stress (24). In an animal model of maternal diabetes induced by streptozotocin, offspring displayed deficits in social behavior (25), whereas in another animal model of GDM, male offspring displayed increased repetitive behaviors (26). RNA analysis showed dysregulation of neurodevelopmental- and immune-related genes in the brain (26). Further research is needed to explain the gradient of risk for ASD among offspring of women with different types of diabetes found in this and other studies.

We found an increased risk of diabetes in children of mothers with both preexisting diabetes and GDM. We could not determine whether the children themselves had type 1 or type 2 diabetes. However, while one may expect mothers with type 1 diabetes to have an increased risk of children with diabetes (primarily type 1 diabetes), we also found an increased risk of diabetes in children of women with type 2 diabetes and those with GDM, suggesting these latter offspring likely have type 2 diabetes. Older studies in the Pima Indigenous population found an increased risk of type 2 diabetes in children of mothers with type 2 diabetes (27), as did a more recent long-term follow-up study of women in Manitoba, Canada, where there was a gradient of risk (28). Similar to our study, offspring of mothers with type 2 diabetes had a higher risk of diabetes, followed by offspring of women with GDM, whose children had a higher risk of diabetes than women without diabetes (28), again suggesting a gradient of risk according to diabetes type.

We found an increased risk of hypertension among offspring of mothers with preexisting diabetes and GDM. The early rise may be due to the higher rate of congenital anomalies found in offspring of women with diabetes, as there is a higher rate of hypertension in these infants. This risk, however, continues to rise, especially after age 16, suggesting other infants are also affected. Others have also found an increased risk of CV risk factors in children of mothers with GDM. A meta-analysis of 24 studies found

offspring of mothers with GDM had an increased risk of elevated systolic blood pressure, BMI *z*-score, and glucose compared with unexposed children (29).

In this population of offspring of women with diabetes in pregnancy, the risk of hypertension and early-onset CVD was increased. This early increase may have been associated with congenital anomalies where the risk of arrhythmias and heart failure are higher, but then the risk rises again after age 14, suggesting other mechanisms may be contributing. While there is good evidence in animal models showing the association of maternal diabetes and the development of CVD in offspring (5), to date few large population-based longitudinal cohort studies have looked at the risk of CVD in children of women with diabetes. One such study assessed >2 million live births in Denmark with 40 years of follow-up (30). Similar to our findings, they found an increased risk of early-onset CVD in offspring of mothers with type 1 diabetes, type 2 diabetes, and those with GDM. This risk was especially marked in offspring of mothers with diabetes complications and those with CVD themselves. The underlying mechanisms for the development of CVD in mothers with diabetes are not yet understood. Animal models of streptozotocin-induced diabetes during pregnancy show that hyperglycemia is associated with proliferations of offspring cardiomyocytes but inhibition of maturation (5). Other studies show changes in mitochondrial dysfunction in the offspring hearts (5). Therefore, while there appears to be an increased risk of CVD in offspring of women with diabetes, more research is needed to better understand underlying mechanisms and possible interventions.

To date there is evidence that children of women with diabetes have an increased incidence of diabetes themselves. However, this increase may be due to genetic and/or environmental influences rather than to the in utero glycemic environment. To try to discern this difference, we evaluated the association of maternal glycemia in pregnancy with these long-term outcomes in the children. We found an independent association between maternal glycemia in women with preexisting diabetes and the development of diabetes, hypertension, and CVD in the offspring. This indicates that hyperglycemia in utero represents a potentially modifiable risk factor for the development of these outcomes in the offspring. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) follow-up study studied maternal glycemia and the risk of impaired glucose tolerance in the offspring of mothers with GDM (31). They found that higher maternal glucose levels at 28 weeks' gestation were associated with impaired glucose tolerance and reduced insulin sensitivity in the children at 11 years of age, after adjustment for confounders, including maternal BMI. In a study of women with type 1 diabetes, higher levels of glucose were associated with the development of type 2 diabetes or prediabetes in offspring (32), suggesting the risk was associated with the in utero milieu rather than a genetic predisposition. Although we did find a gradient of risk for ASD and ADHD in the children of women with diabetes, with the highest risk in offspring of women with type 1 diabetes, we did not find a statistically significant association between the level of maternal glycemia during pregnancy and the development of ASD or ADHD. It may be that the sample size is too small, that the effect is too small to detect, or that other factors, such as genetic/immune-mediated factors, also play a role. Further research is needed to better understand this association.

This study has several strengths. This was a large, population-based cohort study of >3 million pregnancies, with information collected prospectively. Validated algorithms were used to define diabetes in pregnancy. We were able to control for several potential confounders.

There are some limitations, however. Although we adjusted for many confounders, there may be residual confounding. We were not able to adjust for maternal BMI; however, the associations were found in women with type 1 as well as type 2 diabetes and GDM, the former less likely to be confounded by BMI. As well, although the algorithm for ASD has been validated in the literature, validation studies show high specificity but low sensitivity, suggesting they may not be sensitive enough; therefore, we may have underestimated the risk for this outcome (33). The algorithm for ADHD, although used in the literature, may also be underestimating the risk, as some children who are not given prescriptions may only be seen in schools and therefore not found in physician claims (34). More research is needed. We found a slightly higher rate of out-migration among offspring of women without diabetes that may have led to a slight underestimate of event rates. In addition, HbA_{1c} levels in pregnancy may not fully reflect ambient glycemia due to the reduction in red blood cell survival time in pregnancy leading to a reduction in HbA_{1c} levels and the influence of iron deficiency, which may prolong red cell survival leading to a falsely high HbA_{1c} (35). Finally, only approximately half of the women with preexisting diabetes had available HbA_{1c} values during pregnancy because of laboratory participation early on; however, the characteristics of those who did and did not have HbA_{1c} values were similar.

In summary, children of women with diabetes are at increased risk of neurobehavioral and cardiometabolic outcomes, including ADHD, ASD, hypertension, diabetes, and CVD, with a gradient of risk seen depending on diabetes type. Maternal glycemia in women with preexisting diabetes is clearly associated with an increased risk of these long-term cardiometabolic outcomes in offspring, but this association is not clear with regards to the neurobehavioral outcomes. In mothers with diabetes, the level of maternal glycemia represents a potentially modifiable risk factor in preventing cardiometabolic disease in their children.

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manuscript. D.S.F, A.Ar., A.As., P.L., and B.R.S. interpreted the data. D.S.F., A.Ar., P.L., G.L.B., and B.R.S. helped design the study and proposed the analyses. A.As. conducted the analyses. D.S.F. and B.R.S. are the guarantors of this work and as such, had full access to all of the data in the study and take responsibility for the integrity of the data.

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