Role of Type 2 Diabetes in Determining Retinal, Renal, and Cardiovascular Outcomes in Women With Previous Gestational Diabetes Mellitus

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Diabetes Care 2017;40:101–108 | DOI: 10.2337/dc16-1400

OBJECTIVE

Women who have gestational diabetes mellitus (GDM) have elevated lifetime risks for the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), compared with their peers. However, it is not known whether their risk of CVD is dependent upon the development of T2DM. Thus, we sought to evaluate the role of T2DM in determining vascular outcomes in women with previous GDM.

RESEARCH DESIGN AND METHODS

All women in Ontario, Canada, with a live-birth pregnancy between April 1994 and March 2014 (*n* = 1,515,079) were stratified into the following four groups: women with GDM in whom T2DM subsequently developed (*n* = 15,585, median age 32 years); those with GDM in whom T2DM did not develop (*n* = 41,299; median age 32 years); women who did not have GDM but in whom T2DM developed (*n* = 49,397; median age 31 years); and those with neither GDM nor T2DM (*n* = 1,408,798; median age 30 years). Women were followed over a median time of 10.0 years for the development of microvascular and macrovascular outcomes.

RESULTS

Among women who had GDM, only those in whom T2DM developed had an increased risk of vitrectomy/photocoagulation (hazard ratio [HR] 4.49, 95% CI 3.90–5.17), renal dialysis (HR 7.52, 5.24–10.81), and hospitalization for foot infection (HR 4.32, 3.42–5.46) (all $P < 0.0001$). However, for macrovascular outcomes, both women with GDM in whom T2DM developed and those in whom T2DM did not develop had increased risks of CVD (HR 2.82; 2.41–3.30; $P < 0.0001$; and HR 1.30; 1.07–1.59; $P = 0.008$, respectively) and coronary artery disease (HR 3.54; 2.96–4.23; $P < 0.0001$; and HR 1.41; 1.11–1.80; $P = 0.005$, respectively), although absolute event rates were very low.

CONCLUSIONS

Women with GDM have an elevated risk of cardiovascular outcomes, even in the absence of T2DM. In contrast, microvascular risk emerges only in those in whom T2DM develops.

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Received 29 June 2016 and accepted 6 October 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1400/-/DC1.

The diagnosis of gestational diabetes mellitus (GDM) identifies a population of women who have an elevated risk of the development of type 2 diabetes mellitus (T2DM) in the future (1–3). This well-established clinical association between GDM and T2DM is a reflection of their shared pathophysiology (2,3). Specifically, women with GDM have a defect in pancreatic β-cell function that becomes clinically apparent as insufficient compensation for the insulin resistance of late pregnancy, resulting in the antepartum hyperglycemia by which GDM is diagnosed (2,3). After delivery, ongoing worsening of this β-cell defect can be detected as early as the first year postpartum (4,5) and, coupled with insulin resistance, ultimately underlies the risk of subsequent progression over time to prediabetes and T2DM (6–8). In light of this pathophysiology, it is not surprising that GDM is a robust predictor of future T2DM, with affected women exhibiting a greater than sevenfold higher incidence of T2DM, compared with their peers (1).

In recent years, it has emerged that women in whom GDM develops also have an increased future risk of cardiovascular disease (CVD) (9–17). Indeed, despite their relative youth (i.e., being of childbearing age), women with GDM have an elevated risk of clinical CVD events compared with their peers that is apparent within just over a decade after the index pregnancy (15). However, it is not known whether this risk of CVD is dependent upon the development of T2DM (12,13), a distinction that could have implications for appropriate clinical surveillance and risk modification. Specifically, if their cardiovascular risk is entirely dependent upon T2DM, then assessment for glycemic deterioration may be sufficient for vascular screening in this population. Conversely, if their likelihood of CVD is not solely determined by T2DM, then even those individuals whose conditions do not progress to T2DM may warrant surveillance in this regard. Thus, to address this question, we sought to evaluate the role of T2DM in determining vascular outcomes in women with previous GDM.

RESEARCH DESIGN AND METHODS

We conducted a population-based cohort study using health care administrative databases from the Ministry of Health and Long-Term Care of Ontario, Canada. These databases included hospital discharge abstracts from all hospitalizations, physician service claims, and demographic data for all residents eligible for health care in Ontario. Individuals are linked between all data sources through a unique and reproducibly encrypted health card number. The MOMBABY database is derived from the hospitalization data and links hospitalization records of delivering mothers with their newborns. The Ontario Diabetes Database (ODD) is a validated registry of physician-diagnosed nongestational diabetes mellitus that is derived using these data (18). The study was approved by the institutional review board of Sunnybrook Health Sciences Centre.

The study population consisted of all women 15–54 years of age who had a live-birth delivery between April 1994 and March 2014. Women with pregestational diabetes mellitus were identified through the ODD and were excluded from the study, as were women who had previous CVD. For women with multiple eligible pregnancies, one was selected at random. Selecting the most recent pregnancy would have minimized the follow-up time for the study, whereas selecting the first pregnancy (when women were youngest) would have minimized the prevalence of GDM. We therefore selected a random pregnancy for those women with multiple pregnancies so that the impact of these two competing factors on the analysis would be balanced and so that any potential biases relating to birth sequence would be mitigated. Baseline characteristics identified for each woman were age at index delivery, socioeconomic status (ascertained ecologically based on neighborhood household income, divided into quintiles), and rurality of residence (using the Rurality Index of Ontario score) (19).

For each woman, the presence or absence of GDM in the index pregnancy was ascertained from the diagnostic codes associated with the delivery hospitalization, and the development of diabetes mellitus (DM) during the follow-up period was ascertained from postpartum entry into the ODD. Women were divided into four mutually exclusive exposure groups based on these two factors: GDM and then DM, GDM and no DM, no GDM and then DM, no GDM and no DM.

All women were observed for outcome events until March 2015. The primary outcome of interest was a CVD event, defined as a hospitalization for myocardial infarction, acute coronary syndrome, coronary artery bypass surgery, percutaneous coronary intervention (PCI), stroke, transient ischemic attack, or carotid endarterectomy. The other macrovascular outcome, coronary artery disease (CAD) events, was a subset of the primary outcome consisting of hospitalizations for myocardial infarction, acute coronary syndrome, coronary artery bypass surgery or PCI. Microvascular outcomes were *1*) retinopathy procedures (physician service claims for laser photocoagulation or vitrectomy) and *2*) incident dialysis (based on physician service claims, excluding women who were already receiving dialysis prior to pregnancy). We also evaluated hospitalizations for foot infections (hospitalization for foot ulcer, lower extremity cellulitis, or lower extremity osteomyelitis), recognizing that this outcome may have both microvascular (neuropathy) and macrovascular (peripheral vascular) components, the relative contributions of which may vary between individuals.

Baseline characteristics were compared among the four exposure groups. Cumulative incidence curves for the primary outcome and each of the secondary outcomes were constructed as 1 minus the Kaplan-Meier survival curve. Cox proportional hazards regression was used to model the independent association of the exposure group with each outcome, censoring at death, the end of health care eligibility, or the end of follow-up. Models were constructed both unadjusted, and adjusting for age, income, and rurality. Sensitivity analyses were performed for the cardiovascular models with further adjustment for diagnosed hypertension and dyslipidema. Analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

The 1,515,079 women comprising the study population were observed over a median period of 10.0 years and

stratified into four groups, as follows: *1*) those who had GDM and then DM developed during follow-up (GDM and then DM; *n* = 15,585); *2*) those who had GDM but DM did not develop during follow-up (GDM and no DM; *n* = 41,299); *3*) those who did not have GDM but DM developed during follow-up (no GDM and then DM; *n* = 49,397); and *4*) those who did not have GDM or subsequent DM (no GDM and no DM; *n* = 1,408,798). Table 1 shows that age at the index pregnancy was higher in the GDM groups, while socioeconomic status (as measured by income quintile) was lower in the two groups in which DM developed. Diagnosed hypertension was more common in the groups in which DM developed, whereas diagnosed dyslipidemia was more prevalent in the two GDM groups. As shown in Supplementary Table 1, absolute event rates of the study outcomes were all <1/1,000 person-years, except for retinopathy in women with GDM in whom DM subsequently developed, where the rate was 1.1/1,000 person-years (i.e., if 100 such women were observed for a median period of 10 years, one would have retinopathy requiring laser photocoagulation or vitrectomy). Cardiovascular and CAD events were less frequent, although events in women with GDM not followed by DM were ~25% more frequent than in women with neither GDM nor DM. On average, the events occurred ~10 years after the index pregnancy, when the women were in their 40s (Supplementary Table 1).

Microvascular Outcomes

Figure 1 shows the incidence of retinopathy procedures (vitrectomy or photocoagulation) (Fig. 1*A*), initiation of dialysis (Fig. 1*B*), and hospitalization for foot ulcer (Fig. 1*C*) in each of the four groups across the duration of follow-up. The risk of retinopathy procedures was elevated in both of the groups in which DM went on to develop, as follows: *1*) GDM and then DM (HR 5.23; 95% CI 4.55–6.01; $P < 0.0001$); and *2*) no GDM and then DM (HR 2.28; 2.06–2.53; $P < 0.0001$) (Table 2). However, the GDM and no DM group had no increased risk compared with the reference group (no GDM and no DM). These findings were unchanged upon adjustment for age, income, and region of residence (Table 2). The absolute event rates per 1,000 patient-years were 0.22 in the no GDM and no DM group, 0.22 in the GDM and no DM group, 0.54 in the no GDM and then DM group, and 1.13 in the GDM and then DM group (Supplementary Table 1).

The same pattern was seen for the initiation of dialysis, with increased risk in GDM and then DM group (HR 7.72; 95% CI 5.40–11.04; $P < 0.0001$) and the no GDM and then DM group (HR 5.02; 3.99–6.33; $P < 0.0001$), but not in the GDM and no DM group (P = 0.56). Again, the findings were unchanged in the adjusted analysis. The absolute event rates per 1,000 patient-years were 0.023 in the no GDM and no DM group, 0.025 in the GDM and no DM group, 0.13 in the no GDM and then DM group, and 0.18 in the GDM and then DM group (Supplementary Table 1). Finally, the very same pattern applied to hospitalization for foot infection, as well. This risk was elevated in the GDM and then DM group (HR 4.32; 3.42–5.45; $P < 0.0001$) and in the no GDM and then DM group (HR 4.22; 3.73–4.78; $P < 0.0001$), but not in the GDM and no DM group (P = 0.64), with no salient change upon covariate adjustment (Table 2). The absolute event rates per 1,000 patient-years were 0.093 in the no GDM and no DM group, 0.098 in the GDM and no DM group, 0.41 in the no GDM and then DM group, and 0.41 in the GDM and then DM group (Supplementary Table 1). Thus, although event rates were modest, the risk of microvascular outcomes was present only in the women in whom DM went on to develop during postpartum follow-up.

Macrovascular Outcomes

Figure 2 shows the incidence of CVD events (Fig. 2*A*) and CAD events (Fig. 2*B*) in each of the four groups across the follow-up period. As with microvascular outcomes, the risk of CVD events was elevated in both of the groups in

Table 1—Characteristics of the study population stratified into the following four groups: *1*) women who had neither GDM nor subsequent DM, *2*) women who did not have GDM but then developed DM, *3*) women who had GDM but did not develop DM, and *4*) women who had GDM and then subsequent DM

	No GDM and no DM (*N* = 1,408,798)	No GDM and then DM (*N* = 49,397)	GDM and no DM (*N* = 41,299)	GDM and then DM (*N* = 15,585)	*P*
Age (years)	30 (26–34)	31 (27–35)	32 (29–36)	32 (29–36)	<0.001
Income quintile					
Lowest	312,293 (22.2)	15,064 (30.5)	10,788 (26.1)	4,717 (30.3)	<0.001
Second	286,212 (20.3)	10,697 (21.7)	9,065 (21.9)	3,382 (21.7)	
Third	283,435 (20.1)	9,402 (19.0)	8,501 (20.6)	3,085 (19.8)	
Fourth	286,194 (20.3)	8,254 (16.7)	7,516 (18.2)	2,576 (16.5)	
Highest	233,587 (16.6)	5,635 (11.4)	5,154 (12.5)	1,707 (11.0)	
Missing	7,077 (0.5)	345 (0.7)	275 (0.7)	118 (0.8)	
Region of residence					
Urban	1,062,180 (75.4)	39,476 (79.9)	34,402 (83.3)	13,072 (83.9)	<0.001
Semiurban	244,660 (17.4)	6,740 (13.6)	4,857 (11.8)	1,680 (10.8)	
Rural	88,159 (6.3)	2,447 (5.0)	1,571 (3.8)	572 (3.7)	
Missing	13,799 (1.0)	734 (1.5)	469 (1.1)	261 (1.7)	
Hypertension	27,365 (1.9)	2,273 (4.6)	1,794 (4.3)	1,069 (6.9)	<0.001
Dyslipidemia	24,178 (1.7)	1,452 (2.9)	1,600 (3.9)	816 (5.2)	<0.001

Categorical data are presented as *n* (%); age is presented as median (interquartile range).

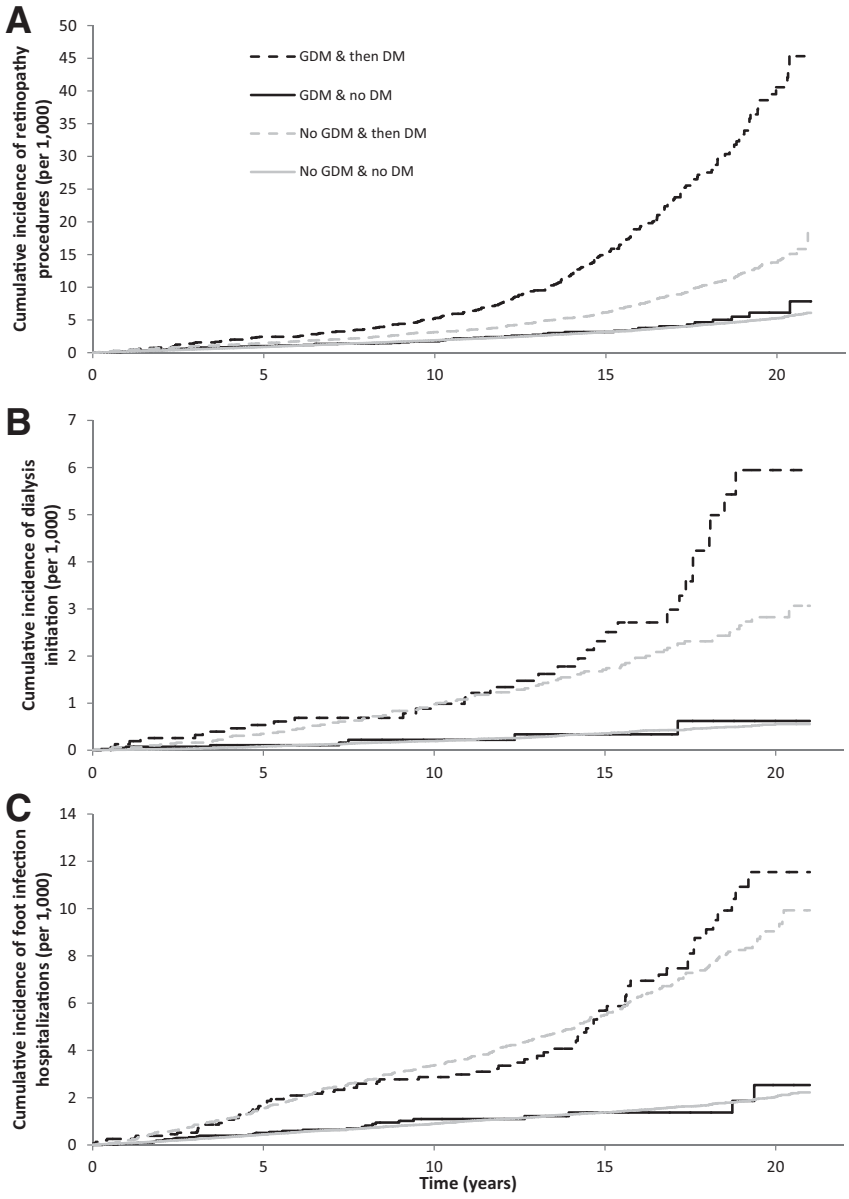

Figure 1—Cumulative incidence of retinopathy procedures (vitrectomy or photocoagulation) (*A*), initiation of renal dialysis (*B*), and hospitalization for foot infection (*C*) in each of the following four groups: *1*) GDM and then DM; *2*) GDM and no DM; *3*) no GDM and then DM; and *4*) no GDM and no DM.

which DM went on to develop: *1*) the GDM and then DM group: HR 3.38; 95% CI 2.89–3.96; $P < 0.0001$; and *2*) the no GDM and then DM group: HR 2.18; 1.98–2.39; $P < 0.0001$ (Table 2). However, unlike with microvascular outcomes, the GDM and no DM group also exhibited an increased risk of CVD events (HR 1.53; 1.26–1.86; $P < 0.0001$). These findings were unchanged upon adjustment for age, income, and region of residence (Table 2). The absolute number of event rates per 1,000 patient-years were 0.26 in the no GDM and no DM group, 0.33 in the GDM and no DM group, 0.67 in the no GDM and then DM group, and 0.89 in the GDM and then DM group (Supplementary Table 1). The same pattern was seen for CAD events, with increased risk in the GDM and then DM group (HR 4.44; 3.72–5.30; $P < 0.0001$), the no GDM and then DM group (HR 2.49; 2.22–2.78; $P < 0.0001$), and the GDM and no DM group (HR 1.73; 1.36–2.20; $P < 0.0001$). Again, these findings were unchanged on the adjusted analysis. The absolute event rates per 1,000 patient-years were 0.16 in the no GDM and no DM group, 0.22 in the GDM and no DM group, 0.47 in the no GDM and then DM group, and 0.70 in the GDM and then DM group (Supplementary Table 1).

Finally, we performed sensitivity analyses with further adjustment for the cardiovascular risk factors of diagnosed hypertension and dyslipidemia. The findings again remained unchanged on these analyses for both CVD and CAD, with increased risks of each outcome in the GDM and then DM group (CVD: HR 2.58; 95% CI 2.20–3.02; $P < 0.0001$; CAD: HR 3.23; 2.70–3.86; $P < 0.0001$), the no GDM and then DM group (CVD: HR 1.90; 1.72–2.08; $P < 0.0001$; CAD: HR 2.12; 1.89–2.38; $P < 0.0001$), and the GDM and no DM group (CVD: HR 1.26; 1.03–1.53; $P = 0.02$; CAD: HR 1.36; 1.06–1.73; $P < 0.01$) (data not shown). We also performed sensitivity analyses in which PCI was not included in the definitions of CVD and CAD. As shown in Supplementary Table 2, the findings were unchanged with the exclusion of PCI. It thus emerges that the risk of macrovascular outcomes of CVD and CAD was elevated in women with GDM, even if T2DM did not develop.

CONCLUSIONS

In this study, we demonstrate that, although absolute event rates are low, the risks of CVD and CAD are highest in women who have GDM in whom T2DM subsequently develops, followed by those in whom T2DM develops in the absence of preceding GDM. Importantly, however, women with GDM in whom T2DM does not develop still have an elevated risk of CVD and CAD. In contrast, the risks of microvascular outcomes of advanced retinopathy procedures, the initiation of renal dialysis, and hospitalization for foot infection are only increased in women in whom T2DM develops. It thus emerges that, in women with GDM, future microvascular risk is dependent upon subsequent T2DM, whereas their macrovascular risk is elevated even in the absence of T2DM.

In an earlier study involving 8,191 women with GDM and 81,262 control subjects, adjustment for the development of T2DM attenuated the relationship between GDM and subsequent CVD, leading to the suggestion that intervening T2DM drives the enhanced cardiovascular risk observed in this population (15). Conversely, however, since

Table 2—HRs with 95% CI for each of the following outcomes: (I) retinopathy procedures, (II) dialysis initiation, (III) hospitalization for foot infection, (IV) CVD events, and (V) CAD events

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
(I) Retinopathy procedures						
GDM and then DM	5.23	(4.55–6.01)	<0.0001	4.49	(3.90–5.17)	<0.0001
GDM and no DM	1.11	(0.88–1.41)	0.39	0.96	(0.75–1.21)	0.71
No GDM and then DM	2.28	(2.06–2.53)	<0.0001	2.16	(1.95–2.40)	<0.0001
No GDM and no DM		Reference			Reference	
(II) Dialysis initiation						
GDM and then DM	7.72	(5.40–11.04)	<0.0001	7.52	(5.24–10.81)	<0.0001
GDM and no DM	1.23	(0.61–2.49)	0.56	1.25	(0.62–2.52)	0.54
No GDM and then DM	5.02	(3.99–6.33)	<0.0001	4.79	(3.80–6.05)	<0.0001
No GDM and no DM		Reference			Reference	
(III) Foot infection hospitalization						
GDM and then DM	4.32	(3.42–5.45)	<0.0001	4.32	(3.42–5.46)	<0.0001
GDM and no DM	1.09	(0.76–1.55)	0.64	1.13	(0.79–1.62)	0.50
No GDM and then DM	4.22	(3.73–4.78)	<0.0001	4.10	(3.62–4.65)	<0.0001
No GDM and no DM		Reference			Reference	
(IV) CVD events						
GDM and then DM	3.38	(2.89–3.96)	<0.0001	2.82	(2.41–3.30)	<0.0001
GDM and no DM	1.53	(1.26–1.86)	<0.0001	1.30	(1.07–1.59)	0.008
No GDM and then DM	2.18	(1.98–2.39)	<0.0001	2.01	(1.82–2.20)	<0.0001
No GDM and no DM		Reference			Reference	
(V) CAD events						
GDM and then DM	4.44	(3.72–5.30)	<0.0001	3.54	(2.96–4.23)	<0.0001
GDM and no DM	1.73	(1.36–2.20)	<0.0001	1.41	(1.11–1.80)	0.005
No GDM and then DM	2.49	(2.22–2.78)	<0.0001	2.25	(2.01–2.52)	<0.0001
No GDM and no DM		Reference			Reference	

For each of the groups, the HR is shown unadjusted and after adjustment for age, income, and region of residence. For each outcome, the reference group is no GDM and no DM.

the atherosclerotic process takes many years to manifest clinically, the emergence of a higher incidence of CVD events in just over a decade after a GDM pregnancy raises the possibility that insufficient time exists for the postpartum development of T2DM to fully account for this pathology. Thus, the current study was designed to address this key question. This study was conducted in a much larger population of >1.5 million women (including 56,884 women with GDM) who were stratified based on both *1*) whether or not they had GDM and *2*) whether or not T2DM subsequently developed. With this approach, it is apparent that incident diabetes indeed amplifies the risk of CVD, as would be expected. More importantly, however, we directly demonstrate that, even if T2DM does not develop, women with GDM still have higher incidence rates of both CVD and CAD events in the first decade postpartum, compared with their peers (although it must be recognized that absolute event rates are low).

After a pregnancy complicated by GDM, it is recommended that women undergo oral glucose tolerance testing to ascertain diabetes status. In clinical practice, however, it is widely recognized that the rates of this recommended postpartum testing remain suboptimal across jurisdictions (20). Accordingly, it is possible and, even likely, that our GDM and no DM group included some women with undiagnosed T2DM. In this regard, the comparison of relative microvascular and macrovascular risks across the four study groups may offer relevant insight. Specifically, it is clear from our analyses that, irrespective of GDM status, women in whom T2DM develops have increased risks for all of the microvascular and macrovascular outcomes under study. As such, any undiagnosed diabetes in the GDM and no DM cohort should effectively increase the likelihood of each of these outcomes within that group. Of note, however, women in the GDM and no DM group exhibited increased risks only for CVD and CAD, and not for the microvascular end points. These findings suggest that undiagnosed T2DM is thus unlikely the underlying basis for their macrovascular risk. As the incidence of impaired glucose tolerance (IGT) is known to be much higher in women with previous GDM than in their peers (8,21), it is possible that the potential cardiovascular risk implications of IGT may be relevant, but this remains conjecture at this time (our administrative data sources do not provide reliable tracking of IGT). The current findings would suggest that, if IGT is indeed contributing to macrovascular risk in this patient population, then it does so without increasing the incidence of microvascular outcomes during the 10 years after the index pregnancy. Furthermore, these data underscore the general concept that the microvascular outcomes are specifically associated with diabetes.

Since their cardiovascular risk is not entirely attributable to T2DM, we need to consider other possible contributors in women with GDM. Although our sensitivity analyses found that clinically diagnosed hypertension and dyslipidemia did not fully account for the observed differential in macrovascular risk, there exists the possibility of their underdiagnosis in young women. In this context,

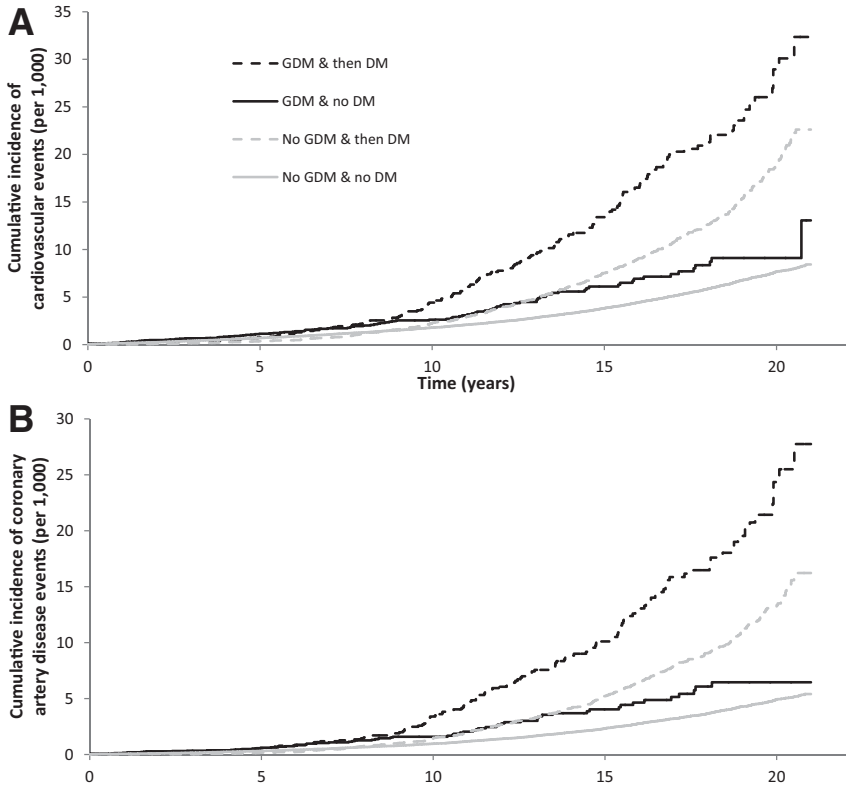

Figure 2—Cumulative incidence of CVD events (*A*) and CAD events (*B*) in each of the following four groups: *1*) GDM and then DM; *2*) GDM and no DM; *3*) no GDM and then DM; and *4*) no GDM and no DM.

it should be noted that several cardiovascular risk factors are known to be more prevalent in women with GDM, compared with their peers (9–13). These features include higher rates of metabolic syndrome, hypertension, elevated levels of C-reactive protein, hypoadiponectinemia, and dyslipidemia (including low levels of HDL cholesterol, and elevated levels of triglycerides, LDL cholesterol, apolipoprotein-B, and small dense LDL particles) (10,22–31). Moreover, the presence of each of the above risk factors in women with GDM has been demonstrated as early as 3 months postpartum (24,28,29), suggesting a chronicity that could provide sufficient duration of exposure to contribute to atherosclerosis. Indeed, a growing body of literature (32–34) suggests that cardiometabolic abnormalities may precede the pregnancy in women in whom GDM develops, the diagnosis of which results from population glucose tolerance screening in the setting of the physiologic stress test posed for the β-cells by the insulin resistance of late gestation (a test that they are destined to fail because of their β-cell defect). In this way, the diagnosis of GDM can be seen as identifying a phenotype with an enhanced lifetime risk not for only T2DM (as per their β-cell defect), but also for CVD (due to a longstanding enhanced cardiovascular risk factor profile).

Although we show that preceding T2DM does not fully account for the incidence of CVD in women with previous GDM, it is clear that the development of T2DM in this patient population yields the greatest cardiovascular risk. Indeed, as shown in Fig. 2 and Table 2, this risk is much higher than that of the no GDM and then DM group, possibly reflecting the impact of differences in the underlying chronic risk factor profile of women in whom GDM develops and in those in whom it does not develop. Furthermore, comparison of the no GDM and then DM group with the GDM and no DM group suggests that the relative impact of incident T2DM on CVD and CAD outcomes likely exceeds that of the cardiovascular risk factor profile of women with GDM.

A limitation of this study is that our administrative data sources do not distinguish between T2DM and type 1 diabetes. However, in women with previous GDM, the vast majority of subsequent diabetes will be T2DM, as per the shared pathophysiology of both conditions. Second, with the median 10-year follow-up period of this study, we cannot exclude the possibility that women with GDM in whom T2DM does not develop may be at increased risk of microvascular outcomes after the first decade postdelivery. In this context, the current data emphasize that screening for the development of T2DM in this patient population may be important for identifying those women who may be at risk for the early presentation of these outcomes in the first decade. Another limitation is that the databases do not track the actual measurements of cardiovascular risk factors such as lipids, A1C, and blood pressure, which might otherwise provide insight into the underlying basis of the enhanced macrovascular risk of women with GDM in whom diabetes does not develop. Conversely, though, the population-based nature of our data has made it possible to study the impact of both GDM and subsequent diabetes in all pregnant women in the population and thereby conclusively demonstrate the latter risk.

As would be expected in a population of young women of childbearing age observed for median period of 10.0 years, the absolute incidence of the vascular outcomes is not very high. Indeed, the absolute event rates were all $<$1/1,000 patient-years (with the exception of the rate of 1.14 for retinopathy procedures in women with GDM and then DM). However, the clinical importance of these data relates to the implications for vascular risk assessment. First, the higher incidence of macrovascular outcomes in women in whom T2DM develops after GDM, compared with those who have no history of preceding GDM, suggest that the former group may warrant a heightened index of suspicion in clinical practice for earlier presentation of CVD. Second, among women who do not have diabetes, the higher incidence of macrovascular outcomes in those with preceding GDM raises the possibility that, despite their relative youth, this patient group potentially may benefit from earlier cardiovascular risk factor assessment

and optimization. Indeed, although their event rates are not very high within the first decade after a pregnancy at a mean age of 32 years, this early presentation of enhanced macrovascular risk suggests that the long-term benefit of risk factor modification may be particularly great in this patient population (one that had not been previously recognized as being at elevated risk, in contrast with individuals with diabetes). It should be noted that, based on the current data, we cannot suggest that early risk factor screening and modification is necessary, as such practices may not be cost effective in such a large patient population in which the absolute risk of cardiovascular events remains low. Rather, the current demonstration that consideration of both GDM history and subsequent DM status stratifies cardiovascular risk even when the incidence is low in the first decade postpartum raises the possibility that this insight could hold relevance for risk factor evaluation and modification later in life, as the women move through middle age and its attendant increase in the incidence of vascular outcomes. Ultimately, the clinical value of such insight and the cost-effectiveness of strategies for acting upon it later in life will need direct evaluation in future studies.

In summary, although event rates are low, women in whom GDM is diagnosed have an elevated risk for the future development of CVD and CAD, whether or not T2DM develops in the years after the pregnancy. Progression to T2DM only modifies the magnitude of this risk increment. In contrast, the risks of advanced retinopathy, nephropathy, and foot infection outcomes are only increased in women in whom T2DM develops. Thus, future macrovascular risk is an inherent feature of GDM, irrespective of subsequent T2DM, whereas microvascular risk emerges only in those in whom T2DM develops.

Funding. R.R. is supported by a Heart and Stroke Foundation of Ontario Mid-Career Investigator Award, and his research program is supported by an Ontario Ministry of Research and Innovation Early Researcher Award. B.R.S. is supported by a Canadian Institutes of Health Research New Investigator award. The Institute for Clinical Evaluative Sciences (ICES) is a nonprofit research institute funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC).

No endorsement by the ICES or the MOHLTC is intended or should be inferred.

The opinions, results, and conclusions reported in this study are those of the authors and are independent from the funding sources.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. R.R. conceived the hypothesis and wrote the manuscript. B.R.S. performed the statistical analyses. Both authors designed the analysis plan, interpreted the data, and critically revised the manuscript for important intellectual content. Both authors approved the final manuscript. B.R.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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