Divergent Trajectories of Cardiovascular Risk Factors in the Years Before Pregnancy in Women With and Without Gestational Diabetes Mellitus: A Population-Based Study

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OBJECTIVE

Women who develop gestational diabetes mellitus (GDM) have an elevated lifetime risk of cardiovascular disease, which has been attributed to an adverse cardiovascular risk factor profile that is apparent even within the first year postpartum. Given its presence in the early postpartum, we hypothesized that this adverse cardiovascular risk factor profile may develop over time in the years before pregnancy.

RESEARCH DESIGN AND METHODS

With population-based administrative databases, we identified all nulliparous women in Ontario, Canada, who had singleton pregnancies between January 2011 and December 2016 and two or more measurements of the following analytes between 2007 and the start of pregnancy: A1C, fasting glucose, random glucose, lipids, and transaminases. This population consisted of 8,047 women who developed GDM and 93,114 women who did not.

RESULTS

The two most recent pregravid tests were performed at a median of 0.61 years and 1.86 years before pregnancy, respectively. Women who went on to develop GDM had higher pregravid A1C, fasting glucose, random glucose, LDL cholesterol, triglycerides, and ALT and lower HDL cholesterol than their peers (all $P < 0.0001$). Notably, in the years before pregnancy, women who went on to develop GDM had higher annual increases than their peers in A1C (1.9-fold higher) (difference 0.0089%/year [95% CI 0.0043–0.0135]) and random glucose (4.3-fold), greater annual decrease in HDL cholesterol (5.5-fold), and lesser annual decline in LDL cholesterol (0.4-fold) (all $P \leq 0.0002$). During this time, fasting glucose and triglycerides increased in women who developed GDM but decreased in their peers (both $P < 0.0001$).

CONCLUSIONS

The adverse cardiovascular risk factor profile of women with GDM evolves over time in the years before pregnancy.

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It has been known for >50 years that the diagnosis of gestational diabetes mellitus (GDM) identifies a population of women who are at risk for ultimately developing type 2 diabetes mellitus (T2DM) (1,2). In the past decade, it has emerged that women with a history of GDM also have an elevated lifetime risk of cardiovascular disease (CVD) (3,4). As demonstrated in a recent meta-analysis (5), women with previous GDM have a twofold higher risk of CVD that emerges within the first decade after pregnancy and is not dependent on the intercurrent development of T2DM. This increased risk of CVD has been attributed to their enhanced cardiovascular risk phenotype, as evidenced by higher prevalence rates of vascular risk factors in the years after delivery (3,6–8). Indeed, by as early as 3 months postpartum, women with recent GDM exhibit higher rates of dysglycemia, hypertension, elevated LDL cholesterol, hypertriglyceridemia, low levels of HDL cholesterol, and metabolic syndrome (9–11). Its presence in the early postpartum raises the possibility that this adverse cardiovascular risk factor profile may have developed over time in the years before pregnancy in this otherwise young healthy patient population. However, little is known about the natural history of cardiovascular risk factors before pregnancy. Thus, our objective in this study was to elucidate the changes over time in cardiovascular risk factors in the years before pregnancy in women who go on to develop GDM and those who do not.

RESEARCH DESIGN AND METHODS

We conducted a population-based retrospective cohort study using real-world data for Ontario, the most populous province in Canada. The databases included records from all hospitalizations in the province and demographic data for all residents eligible for health care in Ontario. The MOMBABY database is derived from hospitalization data and links hospitalization records of delivering mothers with their newborns. The Ontario Diabetes Database is a validated registry of physician-diagnosed non-GDM that is derived using these data (12). The Ontario Laboratory Information System includes data for laboratory test orders and results from community, hospital, and public health laboratories. Laboratories have gradually enrolled in the Ontario Laboratory Information System to contribute their data, starting in 2007. Enrollment generally occurred by region across the province. Individuals are linked among all data sources through unique encoded identifiers.

Population and Variable Definitions

The derivation of the study population is shown in Supplementary Fig. 1. We first identified all nulliparous women aged 20–50 years who had live singleton births between January 2011 and December 2016. Pregnancies with pre-GDM, on the basis of either a record in the Ontario Diabetes Database or pregravid laboratory test results diagnostic for diabetes, were excluded. For each woman, we examined all available laboratory tests from 2007 to the start of pregnancy to find results for A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ALT, and AST. The study cohort consisted of women who had measurement of these analytes on at least two occasions before the start of their pregnancy. In the total population of 309,629 women, there were 208,468 who did not have two or more laboratory measurements and 101,161 with the required tests (Supplementary Fig. 1). As would be expected, those who had the laboratory measurements were slightly older than those who did not (29.8 $\pm$ 4.9 vs. 28.1 $\pm$ 4.8 years). They were also slightly more likely to live in urban areas (81.6% vs. 74.7%), but the women were otherwise similar in ethnicity and income (data not shown).

GDM was defined according to the diagnostic criteria recommended by the Canadian Diabetes Association (now Diabetes Canada) at the time (13). For women in whom antenatal laboratory test data were unavailable, GDM was ascertained on the basis of inclusion of the diagnosis on their delivery hospitalization record. Other baseline characteristics determined at the start of pregnancy were maternal age, income (on the basis of neighborhood median household income), rurality (14), and ethnicity (15).

Statistical Analysis

The study population was stratified into women who developed GDM and those who did not. For each of the exposure variables of interest (pregravid A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ALT, and AST), we compared the mean values in the GDM and non-GDM groups on two occasions: the last measurement before pregnancy and the preceding measurement (Table 1). We also compared the mean adjusted values of these analytes between the groups on both occasions (Table 2) after initial adjustment for age (model 1), followed by additional adjustment for income and rurality (model 2), followed by further adjustment for ethnicity (model 3).

To study the change over time in these pregravid laboratory measurements, we used a linear regression model, estimated using generalized estimating equation methods with the laboratory test result as the dependent variable, and with time, GDM, and the interaction term between time and GDM as independent variables. We assumed an autoregressive correlation structure for the repeated measurements on each subject. Using the β-coefficients of the resultant model, we calculated the slope for the change over time in the laboratory measurement in women with and without GDM (Table 3). We then fit a similar model with adjustment first for age (model 1), followed by additional adjustment for income and rurality (model 2), followed by further adjustment for ethnicity (model 3). We used the slopes and intercepts from the age-adjusted model to plot the estimated trajectory of each laboratory test over 5 years before pregnancy in women with and without GDM. Time was defined in relation to the start of pregnancy. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

RESULTS

Of 314,829 nulliparous women with live singleton births, the study population consisted of 101,161 women in whom the two pregravid tests closest to gestation were performed at a median of 0.61 years and 1.86 years before pregnancy, respectively. Of this study population, 8,047 women went on to develop GDM in pregnancy, and 93,114 did not. As shown in Table 1, women with GDM were

Table 1—Clinical characteristics and pregravid cardiovascular risk factor measurements of the study population, stratified into those who developed GDM and those who did not

Characteristic	No GDM (n = 93,114)	GDM (n = 8,047)	P value
Age (years)	29.7 ± 4.9	31.7 ± 4.9	<0.001
Ethnicity			<0.001
Chinese	6,287 (6.8)	978 (12.2)	
South Asian	4,084 (4.4)	713 (8.9)	
General population	82,743 (88.9)	6,356 (79.0)	
Income quintile			<0.001
Lowest	16,608 (17.8)	1,691 (21.0)	
Second	18,723 (20.1)	1,797 (22.3)	
Third	19,791 (21.3)	1,803 (22.4)	
Fourth	21,128 (22.7)	1,624 (20.2)	
Highest	16,584 (17.8)	1,116 (13.9)	
Missing	280 (0.3)	16 (0.2)	
Rurality			<0.001
Urban	75,546 (81.1)	6,987 (86.8)	
Semiurban	13,687 (14.7)	831 (10.3)	
Rural	3,881 (4.2)	229 (2.8)	
Pregravid cardiovascular risk factors			
A1C (%)			
Measurement before pregnancy	5.35 ± 0.002	5.56 ± 0.006	<0.0001
Preceding measurement	5.34 ± 0.002	5.54 ± 0.006	<0.0001
Fasting glucose (mmol/L)			
Measurement before pregnancy	4.68 ± 0.003	4.95 ± 0.008	<0.0001
Preceding measurement	4.69 ± 0.003	4.92 ± 0.008	<0.0001
Random glucose (mmol/L)			
Measurement before pregnancy	4.80 ± 0.003	5.14 ± 0.011	<0.0001
Preceding measurement	4.79 ± 0.003	5.08 ± 0.011	<0.0001
Total cholesterol (mmol/L)			
Measurement before pregnancy	4.54 ± 0.004	4.74 ± 0.013	<0.0001
Preceding measurement	4.58 ± 0.004	4.76 ± 0.013	<0.0001
LDL cholesterol (mmol/L)			
Measurement before pregnancy	2.52 ± 0.004	2.75 ± 0.011	<0.0001
Preceding measurement	2.56 ± 0.004	2.77 ± 0.011	<0.0001
HDL cholesterol (mmol/L)			
Measurement before pregnancy	1.58 ± 0.002	1.43 ± 0.006	<0.0001
Preceding measurement	1.57 ± 0.002	1.43 ± 0.006	<0.0001
Triglycerides (mmol/L)			
Measurement before pregnancy	0.97 ± 0.003	1.25 ± 0.009	<0.0001
Preceding measurement	1.00 ± 0.003	1.23 ± 0.009	<0.0001
ALT (IU/L)			
Measurement before pregnancy	18.4 ± 0.1	21.7 ± 0.2	<0.0001
Preceding measurement	19.3 ± 0.1	22.5 ± 0.3	<0.0001
AST (IU/L)			
Measurement before pregnancy	21.6 ± 0.1	22.1 ± 0.4	0.26
Preceding measurement	23.4 ± 0.2	23.8 ± 0.7	0.57

Data are mean ± SD or n (%).

slightly older (mean age 31.7 vs. 29.7 years), had a lower socioeconomic status (as indicated by income quintile), and were more likely to be of Chinese or South Asian ethnicity and living in an urban area (all $P < 0.001$). At both the last pregravid test before pregnancy and the preceding measurement, the women who went on to develop GDM had higher A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT and lower HDL cholesterol than did their peers (all $P < 0.0001$).

We next compared mean adjusted values of these pregravid measures between women who developed GDM and those who did not (Table 2) after progressive sequential adjustment for age (model 1), income and rurality (model 2), and ethnicity (model 3). At both pregravid tests and with each of these adjustments, women who developed GDM had a higher mean adjusted A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT and lower HDL cholesterol than women who did not develop GDM (all $P < 0.0001$). Mean adjusted AST did not differ between the groups.

We next sought to determine whether the rate of change over time in these factors differed between women who developed GDM and those who did not. As shown in Table 3, after adjustment for the covariates noted above, the women who went on to develop GDM had higher annual increases than their peers in A1C (1.94-fold higher) and random glucose (4.25-fold), greater annual decrease in HDL cholesterol (5.53-fold), and lesser annual declines in total cholesterol (0.31-fold) and LDL cholesterol (0.42-fold) (all $P \leq 0.0002$). Moreover, during this time, fasting glucose and triglycerides increased in women who developed GDM but decreased in their peers (both $P < 0.0001$). The women with GDM also had a higher annual increase in ALT (2.65-fold, $P = 0.02$), with no difference between the groups in the change in AST. These findings of differential slopes between women with and without GDM for all these analytes were unchanged in *1*) sensitivity analyses in which model 3 was further adjusted for the earliest (baseline) value of the analyte and *2*) sensitivity analyses of model 2 in which women of Chinese and South Asian ethnicity were excluded, thereby yielding a primarily White population (data not shown). It thus emerges that in the years before pregnancy, the trajectories of glycemic measures, lipids, and ALT diverged between women who went on to develop GDM and those who did not.

Figure 1 illustrates the clinical implications for cardiovascular risk factors by showing the predicted trajectories of these measures in the years before pregnancy in a 29-year-old woman who goes on to develop GDM versus a 29-year-old woman who does not develop GDM. These trajectories reveal that the rising A1C over time in women who develop GDM (Fig. 1*A*) is driven by rising random glucose and the absence of the mild decrement in fasting glucose seen in their peers (Fig. 1*B* and *C*). Conversely, the comparative increase in total and LDL cholesterol in the GDM group reflects a lesser decline in these measures than that which occurred in the non-GDM group (Fig. 1*D* and *E*). Finally, the women who developed GDM exhibited a more profound decline in HDL cholesterol in the years before pregnancy (Fig. 1*F*)

Table 2—Mean adjusted values of pregravid cardiovascular risk factors in women who developed GDM and those who did not

Covariate	No GDM	GDM	*P* value
A1C (%)			
Measurement before pregnancy			
Model 1	5.35 ± 0.002	5.55 ± 0.006	<0.0001
Model 2	5.35 ± 0.002	5.54 ± 0.006	<0.0001
Model 3	5.36 ± 0.002	5.54 ± 0.006	<0.0001
Preceding measurement			
Model 1	5.34 ± 0.002	5.54 ± 0.006	<0.0001
Model 2	5.34 ± 0.002	5.53 ± 0.006	<0.0001
Model 3	5.35 ± 0.002	5.53 ± 0.006	<0.0001
Fasting glucose (mmol/L)			
Measurement before pregnancy			
Model 1	4.68 ± 0.003	4.94 ± 0.008	<0.0001
Model 2	4.68 ± 0.003	4.94 ± 0.008	<0.0001
Model 3	4.68 ± 0.003	4.94 ± 0.008	<0.0001
Preceding measurement			
Model 1	4.69 ± 0.003	4.91 ± 0.008	<0.0001
Model 2	4.69 ± 0.003	4.91 ± 0.008	<0.0001
Model 3	4.69 ± 0.003	4.91 ± 0.008	<0.0001
Random glucose (mmol/L)			
Measurement before pregnancy			
Model 1	4.80 ± 0.003	5.13 ± 0.011	<0.0001
Model 2	4.80 ± 0.003	5.12 ± 0.011	<0.0001
Model 3	4.80 ± 0.003	5.12 ± 0.012	<0.0001
Preceding measurement			
Model 1	4.79 ± 0.003	5.07 ± 0.011	<0.0001
Model 2	4.79 ± 0.003	5.07 ± 0.011	<0.0001
Model 3	4.79 ± 0.003	5.07 ± 0.011	<0.0001
Total cholesterol (mmol/L)			
Measurement before pregnancy			
Model 1	4.54 ± 0.004	4.71 ± 0.013	<0.0001
Model 2	4.54 ± 0.004	4.72 ± 0.013	<0.0001
Model 3	4.54 ± 0.004	4.72 ± 0.013	<0.0001
Preceding measurement			
Model 1	4.58 ± 0.004	4.72 ± 0.013	<0.0001
Model 2	4.58 ± 0.004	4.73 ± 0.013	<0.0001
Model 3	4.57 ± 0.004	4.73 ± 0.013	<0.0001
LDL cholesterol (mmol/L)			
Measurement before pregnancy			
Model 1	2.52 ± 0.004	2.73 ± 0.011	<0.0001
Model 2	2.52 ± 0.004	2.73 ± 0.011	<0.0001
Model 3	2.52 ± 0.004	2.73 ± 0.011	<0.0001
Preceding measurement			
Model 1	2.56 ± 0.004	2.75 ± 0.011	<0.0001
Model 2	2.56 ± 0.004	2.74 ± 0.011	<0.0001
Model 3	2.56 ± 0.004	2.75 ± 0.011	<0.0001
HDL cholesterol (mmol/L)			
Measurement before pregnancy			
Model 1	1.58 ± 0.002	1.41 ± 0.006	<0.0001
Model 2	1.58 ± 0.002	1.42 ± 0.006	<0.0001
Model 3	1.58 ± 0.002	1.42 ± 0.006	<0.0001
Preceding measurement			
Model 1	1.57 ± 0.002	1.42 ± 0.006	<0.0001
Model 2	1.57 ± 0.002	1.43 ± 0.006	<0.0001
Model 3	1.57 ± 0.002	1.43 ± 0.006	<0.0001
Triglycerides (mmol/L)			
Measurement before pregnancy			
Model 1	0.97 ± 0.003	1.25 ± 0.009	<0.0001
Model 2	0.97 ± 0.003	1.25 ± 0.009	<0.0001
Model 3	0.97 ± 0.003	1.25 ± 0.009	<0.0001

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coupled with rising triglycerides (in contrast to the mild decline therein seen in their peers) (Fig. 1*G*). Taken together, these dynamic changes yield the evolution over time of an adverse cardiovascular risk factor profile in the years before pregnancy in women who go on to develop GDM.

CONCLUSIONS

In this study, we demonstrate two key findings. First, before pregnancy, women who go on to develop GDM already have higher A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT, along with lower HDL cholesterol, than their peers. Second, these differences arise over time because of divergent trajectories of these risk factors between women who develop GDM and those who do not. It thus emerges that the adverse cardiovascular risk factor profile of women with GDM evolves over time in the years before pregnancy.

There have been few previous studies of pregravid cardiovascular risk factors in women who develop GDM, and these have been limited by examining only single measurements at ~3–7 years before pregnancy and by modest numbers of GDM cases (16–18). Hedderson et al. (16) reported that random glucose measured 7 years before pregnancy predicted GDM in 199 women. Similarly, Harville et al. (17) found that higher triglycerides at 7 years before pregnancy predicted 16 cases of GDM. In the Coronary Artery Risk Development in Young Adults Study, higher fasting glucose and low HDL measured at a median of 33.6 months before pregnancy predicted 154 cases of self-reported GDM in 141 women (18). The current study thus extends these observations with a population-based cohort of 101,161 women (including 8,047 with GDM) in whom pregravid cardiovascular risk factors were measured on at least two occasions at a median of 0.61 and 1.86 years, respectively, before pregnancy. The resultant findings provide a definitive demonstration of differences in glycemia, lipids, and ALT on both occasions between women who go on to develop GDM and those who do not.

Importantly, the current study provides insight into how these differences emerge. Indeed, as shown in Table 3,

Table 2—Continued

Covariate	No GDM	GDM	*P* value
Preceding measurement			
Model 1	1.00 ± 0.003	1.23 ± 0.009	<0.0001
Model 2	1.00 ± 0.003	1.23 ± 0.009	<0.0001
Model 3	1.00 ± 0.003	1.24 ± 0.009	<0.0001
ALT (IU/L)			
Measurement before pregnancy			
Model 1	18.3 ± 0.1	21.7 ± 0.2	<0.0001
Model 2	18.3 ± 0.1	21.7 ± 0.2	<0.0001
Model 3	18.3 ± 0.1	21.7 ± 0.2	<0.0001
Preceding measurement			
Model 1	19.3 ± 0.1	22.5 ± 0.3	<0.0001
Model 2	19.2 ± 0.1	22.5 ± 0.3	<0.0001
Model 3	19.2 ± 0.1	22.6 ± 0.3	<0.0001
AST (IU/L)			
Measurement before pregnancy			
Model 1	21.6 ± 0.1	22.2 ± 0.4	0.16
Model 2	21.6 ± 0.1	22.2 ± 0.4	0.14
Model 3	21.6 ± 0.1	22.2 ± 0.4	0.14
Preceding measurement			
Model 1	23.4 ± 0.2	24.1 ± 0.7	0.37
Model 2	23.4 ± 0.2	24.1 ± 0.7	0.36
Model 3	23.4 ± 0.2	24.1 ± 0.7	0.32

Model 1: adjusted for age. Model 2: model 1 further adjusted for income and rurality. Model 3: model 2 further adjusted for ethnicity.

there are modest differences in the annual rate of change in these cardiovascular risk factors between women who develop GDM and their peers. Over time, these differential rates of change will yield the divergent trajectories (Fig. 1) that cause modest differences to slowly increase in magnitude. As shown in Table 2, by the time of their measurement just before pregnancy, the differences in A1C (~0.2%), fasting and random glucose (~0.2–0.3 mmol/L), total and LDL cholesterol (~0.2 mmol/L), HDL cholesterol (~0.2 mmol/L), and triglycerides (~0.3 mmol/L) are readily apparent between women who go on to develop GDM and their peers. Of note, at this point in their lives (i.e., young nulliparous women in their 20s), the absolute levels of glycemia and lipids are not of a magnitude where one would consider treatment in clinical practice. However, with divergent trajectories, it can be anticipated that, over time, the women who develop GDM will face greater cumulative exposure to these vascular risk factors. The potential clinical significance of such exposure is underscored by the recognition that women with GDM ultimately have a twofold higher risk of CVD than their peers (5). While the current data do not directly link these glycemic and lipid measures to this future risk of CVD, they do suggest a model for how modest differences in risk factors in young adulthood may increase over time and thereby ultimately contribute to clinical vascular disease.

The current findings provide a clear demonstration that although it is diagnosed in pregnancy, GDM is a chronic metabolic disorder that precedes gestation. The clinical manifestation of this condition in pregnancy is due to affected women having a chronic defect in pancreatic β-cell function that results in insufficient compensation for the profound insulin resistance that characterizes the latter half of gestation (thereby yielding the hyperglycemia by which GDM is diagnosed) (19). After pregnancy, progressive worsening of this β-cell defect is the pathophysiologic basis for their increased future risk of T2DM (9,19). Of note, this deterioration of β-cell function manifests primarily in rising postchallenge glycemia (rather than fasting) such that postpartum screening for dysglycemia in this patient population requires an oral glucose tolerance test (rather than fasting glucose measurement) (9,20). In this context, it is notable that the current study reveals that before pregnancy, this patient population also has primarily rising random glucose (rather than fasting), suggesting that the same pathophysiologic process of worsening β-cell function may be unfolding. Indeed, the concept of deteriorating β-cell function over time before pregnancy could provide a pathophysiologic basis for the well-recognized association between higher maternal age and risk of GDM. Although the role of β-cell function cannot be ascertained in this study and, hence, remains conjecture, the current data establish that women who go on to develop GDM undergo concurrent worsening of both glucose and lipid metabolism in the years before pregnancy. Thus, from a life course perspective, the diagnosis of GDM in pregnancy may be viewed as a sentinel event that enables the clinical identification of a population of young women who are on an otherwise unrecognized higher-risk cardiometabolic track than their peers as early as young adulthood (and likely earlier) that may ultimately manifest in CVD later in life.

Strengths of this study include the population-based design using real-world data with multiple measurements of cardiovascular risk factors over time. In addition, the sample size of 101,161 women, with 8,047 who developed GDM, yields robust estimates. While the performance of these laboratory tests as part of clinical care meant that they were not all done at the same time, this large cohort of women with multiple measurements made it possible to study changes over time in these risk factors. A limitation of the study is the lack of data on BMI, which are not captured with the administrative data sources. In this regard, it should be recognized that the smaller previous studies that linked single measurements of pregravid cardiovascular risk factors with future GDM did so with adjustment for BMI (16–18). Moreover, one of the studies noted that neither BMI nor waist circumference before pregnancy remained independently associated with GDM upon inclusion of pregravid lipid and glucose metabolism measures (18).

The current findings hold potential future implications for research and practice. First, these data suggest that higher glycemic and lipid measures in young nulliparous women may enable pregravid identification of those who are at greater risk of GDM. Such identification of high-risk women could provide the capacity for preconception lifestyle intervention and enhanced clinical monitoring in pregnancy (21). Indeed, the

Table 3—Rate of change over time in cardiovascular risk factors in the years before pregnancy in women with and without GDM

Covariate	Without GDM		With GDM		*P* value comparing slopes	Rate of change over time for GDM compared with non-GDM	
	Laboratory value at 5 years pregravid*	Slope (95% CI)	Laboratory value at 5 years pregravid*	Slope (95% CI)		Absolute difference	Relative difference
Change in A1C (% per year)							
Model 1	5.3	0.0098 (0.0082–0.0114)	5.5	0.0188 (0.0143–0.0233)	0.0001	0.0090 (0.0044–0.0136)	1.92×
Model 2	5.3	0.0097 (0.0081–0.0113)	5.5	0.0189 (0.0144–0.0233)	0.0001	0.0091 (0.0045–0.0138)	1.95×
Model 3	5.3	0.0095 (0.0080–0.0111)	5.5	0.0184 (0.0140–0.0229)	0.0002	0.0089 (0.0043–0.0135)	1.94×
Change in fasting glucose (mmol/L per year)							
Model 1	4.7	−0.0097 (−0.0117 to −0.0078)	4.9	0.0089 (0.0023–0.0155)	<0.0001	0.0186 (0.0118–0.0254)	Opposite direction
Model 2	4.7	−0.0101 (−0.0120 to −0.0081)	4.9	0.0085 (0.0019–0.0151)	<0.0001	0.0186 (0.0118–0.0254)	Opposite direction
Model 3	4.7	−0.0101 (−0.0120 to −0.0081)	4.9	0.0085 (0.0019–0.0151)	<0.0001	0.0185 (0.0117–0.0253)	Opposite direction
Change in random glucose (mmol/L per year)							
Model 1	4.8	0.0114 (0.0090–0.0138)	5.0	0.0463 (0.0370–0.0055)	<0.0001	0.0349 (0.0254–0.0444)	4.06×
Model 2	4.8	0.0107 (0.0083–0.0131)	5.0	0.0457 (0.0364–0.0550)	<0.0001	0.0350 (0.0255–0.0445)	4.27×
Model 3	4.8	0.0108 (0.0084–0.0133)	5.0	0.0459 (0.0366–0.0551)	<0.0001	0.0350 (0.0255–0.0445)	4.25×
Change in total cholesterol (mmol/L per year)							
Model 1	4.70	−0.0354 (−0.0381 to −0.0327)	4.78	−0.0102 (−0.0170 to −0.0034)	<0.0001	0.0252 (0.0182–0.0322)	0.29×
Model 2	4.68	−0.0359 (−0.0386 to −0.0332)	4.77	−0.0110 (−0.0178 to −0.0042)	<0.0001	0.0249 (0.0179–0.0319)	0.31×
Model 3	4.70	−0.0357 (−0.0384 to −0.0331)	4.79	−0.0109 (−0.0177 to −0.0041)	<0.0001	0.0249 (0.0179–0.0319)	0.31×
Change in LDL cholesterol (mmol/L per year)							
Model 1	2.66	−0.0306 (−0.0329 to −0.0283)	2.80	−0.0124 (−0.0184 to −0.0063)	<0.0001	0.0183 (0.0121–0.0245)	0.41×
Model 2	2.65	−0.0311 (−0.0334 to −0.0287)	2.79	−0.0129 (−0.0189 to −0.0068)	<0.0001	0.0182 (0.0120–0.0244)	0.41×
Model 3	2.66	−0.0313 (−0.0336 to −0.0290)	2.81	−0.0133 (−0.0193 to −0.0072)	<0.0001	0.0181 (0.0119–0.0242)	0.42×

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Table 3—Continued

Covariate	Without GDM		With GDM		*P* value comparing slopes	Rate of change over time for GDM compared with non-GDM	
	Laboratory value at 5 years pregravid*	Slope (95% CI)	Laboratory value at 5 years pregravid*	Slope (95% CI)		Absolute difference	Relative difference
Change in HDL cholesterol (mmol/L per year)							
Model 1	1.59	−0.0027 (−0.0039 to −0.0015)	1.46	−0.0114 (−0.0143 to −0.0084)	<0.0001	−0.0087 (−0.0117 to −0.0056)	4.22×
Model 2	1.59	−0.0024 (−0.0036 to −0.0012)	1.46	−0.0112 (−0.0141 to −0.0082)	<0.0001	−0.0088 (−0.0118 to −0.0057)	4.67×
Model 3	1.59	−0.0019 (−0.0135 to −0.0076)	1.46	−0.0105 (−0.0135 to −0.0076)	<0.0001	−0.0086 (−0.0117 to −0.0056)	5.53×
Change in triglycerides (mmol/L per year)							
Model 1	1.00	−0.0043 (−0.0064 to −0.0021)	1.15	0.0296 (0.0227–0.0365)	<0.0001	0.0339 (0.0268–0.0409)	Opposite direction
Model 2	0.99	−0.0052 (−0.0074 to −0.0031)	1.15	0.0284 (0.0215–0.0353)	<0.0001	0.0336 (0.0266–0.0407)	Opposite direction
Model 3	1.00	−0.0054 (−0.0076 to −0.0033)	1.16	0.0281 (0.0212–0.0350)	<0.0001	0.0335 (0.0265–0.0406)	Opposite direction
Change in ALT (IU/L per year)							
Model 1	19	0.2472 (0.1440–0.3504)	22	0.6146 (0.3012–0.9281)	0.02	0.3674 (0.0516–0.6833)	2.49×
Model 2	19	0.2240 (0.1214–0.3265)	22	0.5915 (0.2779–0.9051)	0.02	0.3676 (0.0516–0.6835)	2.64×
Model 3	19	0.2227 (0.1200–0.3254)	22	0.5901 (0.2767–0.9035)	0.02	0.3674 (0.0515–0.6833)	2.65×
Change in AST (IU/L per year)							
Model 1	24	0.1214 (−0.0610 to 0.3038)	25	0.3143 (−0.3220 to 0.9507)	0.56	0.1929 (−0.4573 to 0.8432)	No significant difference
Model 2	24	0.1125 (−0.0666 to 0.2915)	25	0.3016 (−0.3341 to 0.9373)	0.57	0.1892 (−0.4601 to 0.8384)	No significant difference
Model 3	23	0.1110 (−0.0681 to 0.2901)	25	0.3003 (−0.3347 to 0.9352)	0.57	0.1892 (−0.4594 to 0.8379)	No significant difference

Model 1: adjusted for age. Model 2: model 1 further adjusted for income and rurality. Model 3: model 2 further adjusted for ethnicity. *Laboratory values at 5 years pregravid are estimated from the model for a general population of women at the cohort mean age of 29.8 years living in an urban area with an income in the third quintile.

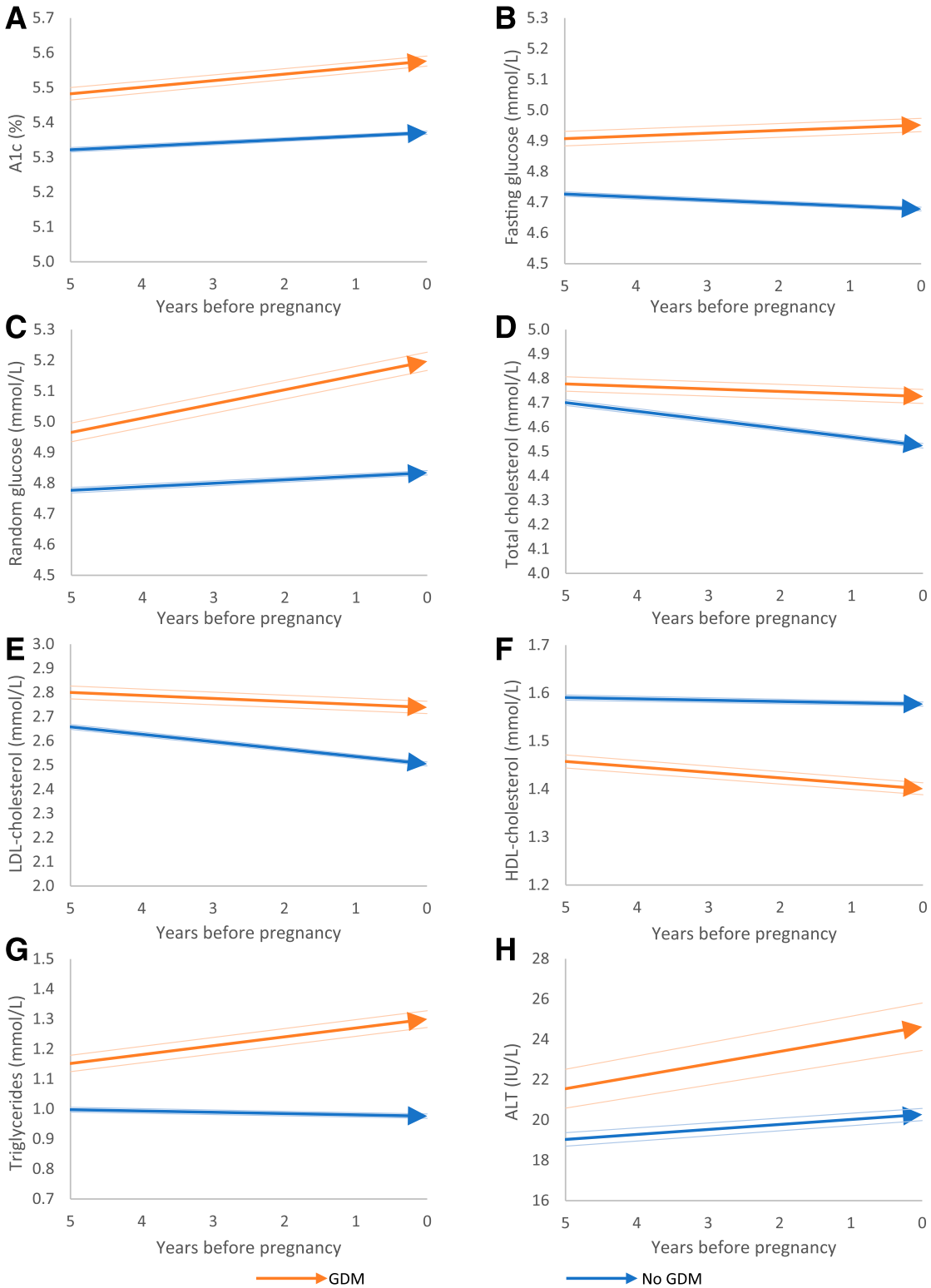

Figure 1—Predicted trajectories of the following cardiovascular risk factors in the years before pregnancy in a 29-year-old woman who goes on to develop GDM and in one who does not. *A*: A1C. *B*: Fasting glucose. *C*: Random glucose. *D*: Total cholesterol. *E*: LDL cholesterol. *F*: HDL cholesterol. *G*: Triglycerides. *H*: ALT.

potential importance of early identification is underscored by growing recognition that intrauterine biochemical changes (22) and fetal overgrowth (23) can precede the clinical diagnosis of GDM in late second trimester. Second, in demonstrating adverse trajectories of cardiovascular risk factors at a young age in a patient population that is known to have an elevated lifetime risk of CVD, the current data suggest that these factors may warrant closer postpartum surveillance in women

who are diagnosed with GDM. This concept would align with a recent call from the American College of Obstetricians and Gynecologists for a new paradigm of individualized postpartum care to improve long-term health in women (24,25).

In summary, even before pregnancy, there are clear differences in cardiovascular risk factors between women who go on to develop GDM and those who do not. Specifically, women who develop GDM have higher pregravid A1C, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT coupled with lower HDL cholesterol. These differences arise because of divergent pregravid trajectories in women who develop GDM and their peers. It thus emerges that from a life course perspective, the diagnosis of GDM identifies a population of women who are already on a higher-risk cardiometabolic track than their peers in young adulthood, one that may contribute to their elevated risk of CVD later in life.

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