Journal of the American Heart Association

ORIGINAL RESEARCH

Patterns of Cardiovascular Risk Factors in the Years Before Pregnancy in Nulliparous Women With and Without Preterm Birth and Small-for-Gestational-Age Delivery

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BACKGROUND: Women with either preterm or small-for-gestational-age (SGA) delivery have an elevated lifetime risk of cardiovascular disease that has been attributed to the accrual of vascular risk factors over time. We sought to determine whether an adverse cardiovascular risk factor profile develops in the years before pregnancies complicated by preterm delivery or SGA.

METHODS AND RESULTS: Using administrative databases, we identified all 156 278 nulliparous women in Ontario, Canada, who had singleton pregnancies between January 2011 and December 2018 and ≥2 measurements of the following analytes between January 2008 and the start of pregnancy: glycosylated hemoglobin, glucose, lipids, and alanine aminotransferase. There were 11 078 women with preterm delivery and 19 367 with SGA. The 2 most recent pregravid tests were performed at median 0.6 (interquartile range, 0.3–1.4) and 1.9 (interquartile range, 1.1–3.3) years before pregnancy, respectively. Women with preterm delivery had higher pregravid glycosylated hemoglobin, glucose, low-density lipoprotein cholesterol, triglycerides, and alanine aminotransferase, and lower high-density lipoprotein cholesterol, than those without preterm delivery. In contrast, women with SGA had lower pregravid fasting glucose, random glucose, and triglycerides than those without SGA. In the years before pregnancy, women with preterm delivery had higher annual increases than their peers in glycosylated hemoglobin (0.7-times higher), triglycerides (7.9-times higher), and alanine aminotransferase (2.2-times higher). During this time, fasting glucose increased in women who developed preterm delivery but decreased in their peers.

CONCLUSIONS: An adverse cardiovascular risk factor profile evolves over time in the years before pregnancy complicated by preterm delivery, but does not necessarily precede SGA.

Key Words: A1c ■ glucose ■ lipids ■ preconception ■ pregravid ■ preterm ■ small-for-gestational-age

In the past decade, there has been growing recognition that the maternal physiologic response to pregnancy can identify women who are at risk of developing cardiovascular disease (CVD) later in life.[1–3] Notably, pregnancy outcomes such as preterm delivery, delivery of a small-for-gestational-age (SGA) infant, gestational diabetes mellitus, and pre-eclampsia identify women who have an elevated lifetime risk of CVD.[4–10] Indeed, women with preterm delivery (defined as length of gestation <37 weeks) have an ≈2-fold increase in the risk of CVD.[1,2] This increased risk has been partly attributed to an adverse cardiovascular risk phenotype, as evidenced by studies showing that women with a history of preterm delivery have higher prevalence rates of vascular risk factors, including dyslipidemia, dysglycemia, hypertension, and metabolic syndrome.[9,11–15] Importantly, previous studies have also noted lipid abnormalities and higher glucose in the years before a pregnancy complicated by preterm delivery,[16,17] although conflicting findings have also

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.021321

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Before pregnancy, women who go on to have preterm delivery have higher glycosylated hemoglobin, fasting glucose, low-density lipoprotein cholesterol, triglycerides, and alanine aminotransferase, along with lower high-density lipoprotein cholesterol, than their peers.
- These differences arise over time because of distinct trajectories of these risk factors between women who develop preterm delivery and those who do not.
- In contrast, women who have a small-for-gestational-age delivery exhibit neither an adverse pregravid cardiovascular risk factor profile nor evidence of the evolution thereof in the years before pregnancy.

What Are the Clinical Implications?

- An adverse cardiovascular risk factor profile evolves over time in the years before pregnancy complicated by preterm delivery but does not necessarily precede small-for-gestational-age delivery.
- Although both diagnoses identify women at risk of future cardiovascular disease, the early-life evolution of this later-life cardiovascular risk differs between women with preterm birth and those with small-for-gestational-age delivery.

Nonstandard Abbreviations and Acronyms

OLIS	Ontario Laboratory Information System

been reported.[18] In this context, we sought to evaluate the patterns and changes over time in cardiovascular risk factors in the years before pregnancies in which preterm delivery or SGA occurred. Our objective was to determine whether an adverse cardiovascular risk factor profile develops over time in the years before pregnancies complicated by either preterm delivery or SGA.

METHODS

We conducted a 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 the hospitalization data and links hospitalization records of delivering mothers with their newborns. The Ontario Laboratory Information System (OLIS) includes data for laboratory test orders and results from community, hospital, and public health laboratories. Laboratories have gradually enrolled in OLIS to contribute their data, starting in 2007. Enrollment generally occurred by region across the province. These databases were linked using unique encoded identifiers and analyzed at ICES (formerly the Institute for Clinical Evaluative Sciences). The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (eg, healthcare 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 (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Population and Variable Definitions

The derivation of the study population is shown in Figure S1. We first identified all nulliparous women aged 20 to 50 years inclusive who had live singleton births between January 2011 and December 2018. Pregnancies with pregestational diabetes mellitus, based either on a record in the Ontario Diabetes Database[19] or on pregravid laboratory test results diagnostic for diabetes mellitus, were excluded. For each woman, we examined all available laboratory tests from January 2008 to the start of pregnancy to identify results for glycosylated hemoglobin (A1c), fasting glucose, random glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and alanine aminotransferase (ALT). The study cohort consisted of women who had measurement of at least 1 of these analytes on at least 2 occasions before the start of their pregnancy. In the total population of 413 690 women, there were 257 412 who did not have ≥2 laboratory measurements and 156 278 with the required tests (Figure S1). The women who had ≥2 laboratory measurements were slightly older than those who did not (30.6±4.9 versus 28.9±4.7 years), more likely to have hypertension (2.9% versus 1.1%), and more likely to have dyslipidemia (3.6% versus 0.9%) but the women were otherwise similar in ethnicity, income, and length of gestation (data not shown). Sample sizes for individual analytes ranged from 37 517 to 114 998 (Table S1).

Baseline characteristics determined at the start of pregnancy were maternal age, ethnicity,[20] income

(based on neighborhood median household income), and rurality.[21] Preterm delivery was defined by gestational age at delivery <37 weeks. SGA was defined by birthweight <10th centile for gestational age based on sex-specific tables for the Canadian population.[22] Length of gestation and birthweight are directly abstracted from hospital records into the Discharge Abstracts Database. While they are mandatory fields, there have not been any re-abstraction studies to validate the accuracy of these fields.

Statistical Analysis

The study population was stratified in 2 ways: (1) women with preterm delivery and women who did not have preterm delivery, and (2) women who delivered an SGA neonate and those whose baby was not SGA. For each of the exposure variables of interest (pregravid A1c, fasting glucose, random glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and ALT), we compared the mean values within these 2 stratifications on 2 occasions: the last measurement before pregnancy and the preceding measurement (Table 1). On both occasions, we also compared the mean adjusted values of these analytes between those with and without preterm delivery and between those with and without SGA, after adjustment for age, ethnicity, income, and rurality (Table 2). These analyses were also further adjusted for pre-eclampsia, which occurred in 3827 women (Table S2).

To study the change over time in these pregravid laboratory measurements, we used generalized estimating equations for a continuous outcome to account for the repeated measures, assuming an autoregressive covariance structure. The laboratory test result was the dependent variable, with time, preterm delivery (or SGA), and the interaction term between time and preterm delivery (or SGA) as independent variables. We assumed an autoregressive correlation structure for the repeated measurements on each subject because laboratory values are ordered in time. Using the beta-coefficients of the resultant model, we calculated the slope for the change over time in the laboratory measurement (1) in women with and without preterm delivery and (2) in women with and without SGA (Table 3). The models were adjusted for age, ethnicity, income, and rurality. 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 preterm delivery (Figure) and in women with and without SGA (Figure S2). Time was defined in relation to the start of pregnancy. We used the Genmod procedure in SAS Enterprise Guide version 7.15 for this analysis.

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

The study population consisted of 156 278 women, in whom the 2 pregravid tests closest to gestation were performed at median 0.6 (interquartile range, 0.3–1.4) and 1.9 (interquartile range, 1.1–3.3) before pregnancy, respectively. The women completed laboratory tests a mean 4.0±3.3 times in the years before pregnancy. Within this study population, 11 078 women went on to have preterm delivery and 19 367 women delivered an SGA neonate (there were 123 women in whom SGA status could not be ascertained). Table 1 shows the comparisons (1) between women with and without preterm delivery and (2) between women with and without SGA, respectively. Compared with their peers, women with SGA were more likely to be of South Asian ethnicity and living in an urban area (both $P<0.001$). Length of gestation was also slightly shorter in those with SGA (mean 38.7±2.0 versus 39.0±1.9 weeks, $P<0.001$).

At both the last pregravid test before pregnancy and the preceding measurement, women who went on to have preterm delivery had higher A1c, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT, and lower HDL cholesterol, than did their peers (all $P\leq0.005$) (Table 1). In contrast, women with SGA had lower fasting glucose, random glucose, and triglycerides than their peers (all $P\leq0.003$). These relative differences in their respective cardiovascular risk factor profiles were further amplified after adjustment for age, ethnicity, income, and rurality (Table 2). Indeed, at both pregravid tests, women with preterm delivery had higher mean adjusted A1c, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT, and lower HDL cholesterol, than women who did not deliver preterm (all $P<0.0001$). These findings were unchanged upon further adjustment for pre-eclampsia (Table S2). These findings were also unchanged after exclusion of women with hypertension (Table S3) and after exclusion of those with dyslipidemia (Table S4). In contrast, at both pregravid tests, women with SGA had lower mean adjusted fasting glucose, random glucose, and triglycerides than those without SGA (all $P\leq0.0005$). These findings were also unchanged upon further adjustment for pre-eclampsia (Table S2) and after exclusion of women with hypertension and

Table 1. Demographic and Clinical Characteristics of the Study Population, Stratified 2 Ways: (1) Those With and Without Preterm Delivery and (2) Those With and Without SGA Delivery

Characteristics	Not Preterm (n=145 200)	Preterm (n=11 078)	*P* Value	Not SGA (n=136 788)	SGA (n=19 367)	*P* Value
Age, y	30.6±4. 9	31.1±5.2	<0.001	30.6±4.9	30.7±5.0	<0.001
Ethnicity			<0.001			<0.001
Chinese	9986 (6.9%)	608 (5.5%)		9002 (6.6%)	1590 (8.2%)	
South Asian	6873 (4.7%)	604 (5.5%)		5919 (4.3%)	1551 (8.0%)	
General population	128 341 (88.4%)	9866 (89.1%)		121 867 (89.1%)	16 226 (83.8%)	
Income quintile			<0.001			<0.001
Lowest	25 676 (17.7%)	2218 (20.0%)		24 005 (17.5%)	3865 (20.0%)	
Second	29 136 (20.1%)	2169 (19.6%)		27 255 (19.9%)	4022 (20.8%)	
Third	31 269 (21.5%)	2486 (22.4%)		29 571 (21.6%)	4161 (21.5%)	
Fourth	33 138 (22.8%)	2360 (21.3%)		31 317 (22.9%)	4150 (21.4%)	
Highest	25 625 (17.6%)	1802 (16.3%)		24 293 (17.8%)	3117 (16.1%)	
Missing	356 (0.2%)	43 (0.4%)		362 (0.2%)	52 (0.2%)	
Rurality			0.52			<0.001
Urban	116 123 (80.0%)	8844 (79.8%)		108 675 (79.4%)	16 192 (83.6%)	
Semi-urban	22 339 (15.4%)	1672 (15.1%)		21 608 (15.8%)	2382 (12.3%)	
Rural	6738 (4.6%)	562 (5.1%)		6505 (4.8%)	793 (4.1%)	
Length of gestation, wk	39.3±1.2	33.9±3.2	<0.001	39.0±1.9	38.7±2.0	<0.001
Pregravid biochemistry						
A1c (%)						
Measurement before pregnancy	5.31±0.002	5.37±0.006	<0.0001	5.31±0.002	5.33±0.004	0.0002
Preceding measurement	5.34±0.002	5.39±0.005	<0.0001	5.34±0.002	5.36±0.004	0.0002
Fasting glucose, mmol/L						
Measurement before pregnancy	4.72±0.002	4.76±0.008	<0.0001	4.73±0.002	4.68±0.006	<0.0001
Preceding measurement	4.70±0.002	4.73±0.008	0.005	4.71±0.002	4.66±0.006	<0.0001
Random glucose, mmol/L						
Measurement before pregnancy	4.88±0.003	4.94±0.010	<0.0001	4.88±0.003	4.86±0.007	0.003
Preceding measurement	4.84±0.003	4.89±0.009	<0.0001	4.85±0.003	4.82±0.007	<0.0001
Total cholesterol, mmol/L						
Measurement before pregnancy	4.54±0.003	4.66±0.012	<0.0001	4.55±0.003	4.54±0.009	0.049
Preceding measurement	4.56±0.003	4.67±0.012	<0.0001	4.57±0.003	4.54±0.009	0.007
LDL cholesterol, mmol/L						
Measurement before pregnancy	2.52±0.003	2.62±0.010	<0.0001	2.53±0.003	2.52±0.008	0.21
Preceding measurement	2.54±0.003	2.64±0.011	<0.0001	2.55±0.003	2.54±0.008	0.15
HDL cholesterol, mmol/L						
Measurement before pregnancy	1.57±0.002	1.53±0.006	<0.0001	1.57±0.002	1.57±0.004	0.22
Preceding measurement	1.56±0.002	1.52±0.006	<0.0001	1.56±0.002	1.56±0.004	0.44
Triglycerides, mmol/L						
Measurement before pregnancy	1.01±0.002	1.12±0.009	<0.0001	1.02±0.002	0.99±0.006	<0.0001
Preceding measurement	1.02±0.002	1.13±0.009	<0.0001	1.03±0.003	0.99±0.006	<0.0001
Alanine aminotransferase, IU/L						
Measurement before pregnancy	18.6±0.1	20.1±0.2	<0.0001	18.8±0.1	18.3±0.2	0.01
Preceding measurement	19.4±0.1	21.0±0.3	<0.0001	19.6±0.1	18.9±0.2	0.005

Continuous variables are presented as mean±SE. Categorical variables are presented as n (%). A1c indicates glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SGA, small-for-gestational age.

dyslipidemia, respectively (Tables S3 and S4). Thus, women who went on to preterm delivery had an adverse cardiovascular risk factor profile before pregnancy as compared with their peers, whereas women who went on to SGA had a slightly better pregravid risk factor profile than that of their peers.

Table 2. Mean Adjusted Values of Pregravid Cardiometabolic Risk Factors in (1) Women With and Without Preterm Delivery and (2) Women With and Without SGA Delivery, After Adjustment for Age, Ethnicity, Income, and Rurality

	Not Preterm	Preterm	*P* Value	Not SGA	SGA	*P* Value
A1c, %						
Measurement before pregnancy	5.31±0.002	5.36±0.006	<0.0001	5.31±0.002	5.32±0.004	0.13
Preceding measurement	5.35±0.005	5.39±0.007	<0.0001	5.35±0.005	5.36±0.006	0.16
Fasting glucose, mmol/L						
Measurement before pregnancy	4.73±0.002	4.76±0.008	<0.0001	4.73±0.002	4.69±0.006	<0.0001
Preceding measurement	4.69±0.007	4.70±0.010	0.052	4.70±0.007	4.65±0.009	<0.0001
Random glucose, mmol/L						
Measurement before pregnancy	4.88±0.003	4.93±0.010	<0.0001	4.89±0.003	4.86±0.008	0.0005
Preceding measurement	4.84±0.009	4.89±0.013	<0.0001	4.85±0.009	4.82±0.011	<0.0001
Total cholesterol, mmol/L						
Measurement before pregnancy	4.55±0.004	4.65±0.012	<0.0001	4.56±0.004	4.54±0.009	0.03
Preceding measurement	4.55±0.010	4.65±0.015	<0.0001	4.56±0.010	4.54±0.013	0.03
LDL cholesterol, mmol/L						
Measurement before pregnancy	2.52±0.003	2.61±0.010	<0.0001	2.53±0.003	2.51±0.008	0.05
Preceding measurement	2.54±0.009	2.62±0.014	<0.0001	2.55±0.009	2.53±0.012	0.11
HDL cholesterol, mmol/L						
Measurement before pregnancy	1.57±0.002	1.53±0.006	<0.0001	1.57±0.002	1.58±0.004	0.02
Preceding measurement	1.55±0.005	1.51±0.007	<0.0001	1.55±0.005	1.56±0.006	0.06
Triglycerides, mmol/L						
Measurement before pregnancy	1.01±0.003	1.12±0.009	<0.0001	1.02±0.003	0.99±0.007	<0.0001
Preceding measurement	1.01±0.007	1.11±0.011	<0.0001	1.02±0.007	0.98±0.010	<0.0001
Alanine aminotransferase, IU/L						
Measurement before pregnancy	18.8±0.1	20.2±0.2	<0.0001	18.9±0.1	18.5±0.2	0.02
Preceding measurement	19.6±0.3	21.2±0.4	<0.0001	19.8±0.3	19.3±0.3	0.02

Data presented as adjusted mean±SE. A1c indicates glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SGA, small-for-gestational age.

We next sought to determine whether the rate of change over time in these cardiometabolic factors differed between women with preterm delivery and SGA, and their respective peers. As shown in Table 3, in the years before pregnancy, the women who went on to have preterm delivery had higher annual increases than their peers in triglycerides (7.9-fold higher; *P*=0.007) and ALT (2.2-fold; *P*=0.02). Moreover, during this time, fasting glucose increased in women who had preterm delivery but decreased in their peers (*P*=0.04), while A1c decreased less in the former group than in the latter (*P*=0.04). These findings were unchanged upon further adjustment for pre-eclampsia (data not shown). In contrast, before pregnancy, women who went on to have an SGA delivery had an increase in HDL cholesterol while their peers experienced a decrease (*P*=0.003), with no other differential changes in pregravid cardiovascular risk factors. These findings were again unchanged upon further adjustment for pre-eclampsia (data not shown).

Figure illustrates the clinical implications of these analyses by showing the predicted trajectories of

Table 3. Rate of Change Over Time in Cardiometabolic Risk Factors in the Years Before Pregnancy in (Top Panel) Women With and Without Preterm Delivery and (Bottom Panel) in Women With and Without SGA Delivery, Adjusted for Age, Ethnicity, Income, and Rurality

	Not Preterm Delivery		Preterm Delivery			*P* Value Comparing Slopes	Relative Difference in Rate of Change Over Time
Preterm Delivery	Slope	95% CI	Slope	95% CI	χ^2		
Change in A1c, %/y	−0.0113	−0.0123 to −0.0102	−0.0079	−0.0111 to −0.0047	4.11	0.04	0.7 x
Change in fasting glucose, mmol/L/y	−0.0022	−0.0035 to −0.0008	0.0027	−0.0018 to 0.0071	4.28	0.04	Opposite directions
Change in random glucose, mmol/L/y	0.0249	0.0233 to 0.0265	0.0292	0.0239 to 0.0345	2.39	0.12	No significant difference
Change in total cholesterol, mmol/L/y	−0.0236	−0.0255 to −0.0217	−0.0194	−0.0247 to −0.0140	2.36	0.12	No significant difference
Change in LDL cholesterol, mmol/L/y	−0.0233	−0.0249 to −0.0216	−0.0213	−0.0259 to −0.0167	0.66	0.42	No significant difference
Change in HDL cholesterol, mmol/L/y	−0.0007	−0.0016 to 0.0002	−0.0028	−0.0053 to −0.0003	2.69	0.10	No significant difference
Change in triglyceride, mmol/L/y	0.0010	−0.0005 to 0.0026	0.0083	0.0030 to 0.0135	7.26	0.007	7.9 x
Change in ALT, IU/L/y	0.2481	0.1503 to 0.3460	0.5499	0.2923 to 0.8076	5.19	0.02	2.2 x

	Not SGA Delivery		SGA Delivery			*P* Value Comparing Slopes	Relative Difference in Rate of Change Over Time
SGA Delivery	Slope	95% CI	Slope	95% CI	χ^2		
Change in A1c (%/y)	−0.0109	−0.0119 to −0.0098	−0.0127	−0.0152 to −0.0103	1.98	0.16	No significant difference
Change in fasting glucose, mmol/L/y	−0.0017	−0.0031 to −0.0003	−0.0031	−0.0064 to 0.0002	0.58	0.45	No significant difference
Change in random glucose, mmol/L/y	0.0252	0.0235 to 0.0268	0.0252	0.0208 to 0.0296	0.00	0.98	No significant difference
Change in total cholesterol, mmol/L/y	−0.0238	−0.0257 to −0.0218	−0.0221	−0.0262 to −0.0180	0.61	0.44	No significant difference
Change in LDL cholesterol, mmol/L/y	−0.0229	−0.0246 to −0.0212	−0.0260	−0.0296 to −0.0225	2.85	0.09	No significant difference
Change in HDL cholesterol, mmol/L/y	−0.0012	−0.0020 to −0.0003	0.0017	−0.0001 to 0.0036	8.62	0.003	Opposite directions
Change in triglyceride, mmol/L/y	0.0010	−0.0006 to 0.0026	0.0034	0.0003 to 0.0065	2.10	0.15	No significant difference
Change in ALT, IU/L/y	0.2747	0.1728 to 0.3766	0.2217	0.0745 to 0.3689	0.45	0.50	No significant difference

A1c indicates glycosylated hemoglobin; ALT, alanine aminotransferase; gluc, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; rand, random; and SGA, small-for-gestational-age.

cardiovascular risk factors in the years before pregnancy in a 30.6-year-old woman from the general population and the middle-income quintile who goes on to have preterm delivery versus one who does not deliver preterm (30.6 years being the median age in the study population). These trajectories reveal that, during the 5 years before pregnancy, women who go on to preterm delivery have rising levels of triglycerides (Figure [G]), fasting glucose (Figure [B]), and ALT (Figure [H]), as compared with their peers, coupled with lesser decline in A1c (Figure [A]). They also maintain higher random glucose (Figure [C]), total cholesterol (Figure [D]), and LDL cholesterol (Figure [E]), coupled with lower HDL (Figure [F]), although these analytes are not changing differentially over time as compared with their peers. This adverse cardiovascular risk factor profile and the evolution thereof stands in stark contrast to that which is observed when comparing women with SGA to their peers (Figure S2). Indeed, in the years before pregnancy, women who go on to an SGA delivery have lower fasting glucose, random glucose, triglycerides, and ALT than their peers and none of these analytes are changing differentially over time. The only differential change over time is a slight increase in HDL in women who go on to SGA. Thus, with SGA, there is neither an adverse pregravid cardiovascular risk factor profile nor evidence of the evolution thereof in the years before pregnancy.

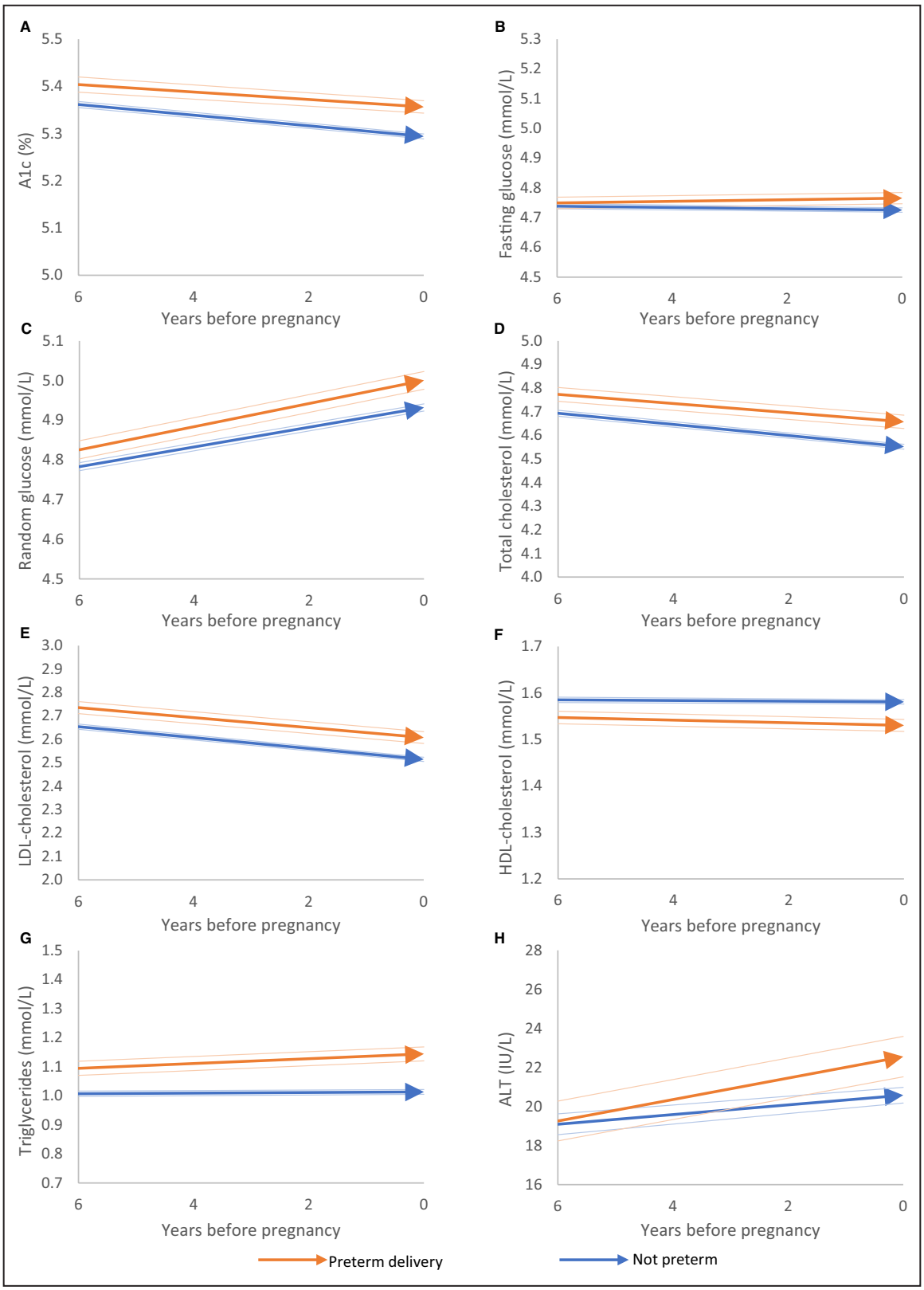

Figure. Predicted trajectories of the following cardiometabolic risk factors in the years before pregnancy in a 30.6-year-old woman from the general population and the middle-income quintile who goes on to have preterm delivery and 1 who does not.

A, A1c, (**B**) fasting glucose, (**C**) random glucose, (**D**) total cholesterol, (**E**) LDL cholesterol, (**F**) HDL cholesterol, (**G**) triglycerides, and (**H**) ALT. A1c indicates glycosylated hemoglobin; ALT, alanine aminotransferase; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

Lastly, recognizing that some women with preterm delivery will also have an SGA neonate, we stratified the study population into the following 4 groups, based on the presence/absence of these conditions: (1) women with SGA only (n=11 670; 11.3%), (2) those with neither SGA nor preterm delivery (n=127 503; 81.7%), (3) women with both SGA and preterm delivery (n=1697; 1.1%), and (4) those with preterm delivery only (n=9285; 5.9%). As shown in Table S5, the mean adjusted values of total cholesterol, LDL cholesterol, triglycerides, and ALT progressively increased (and mean adjusted HDL progressively decreased) across these groups from women with SGA only to those with neither SGA nor preterm delivery to those with both SGA and preterm delivery to women with preterm delivery only (all $P<0.0001$). While this precise progression was not maintained for glucose and A1c, the glycemic measures followed the general pattern wherein women who went on to have preterm delivery had the highest values, while those with SGA had the lowest levels.

DISCUSSION

In this study, we demonstrate 3 key findings. First, before pregnancy, women who go on to preterm delivery already have higher A1c, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT, along with lower HDL cholesterol, than their peers. Second, the differences in triglycerides, A1c, fasting glucose, and ALT arise over time because of divergent trajectories of these risk factors in the years before pregnancy between women who go on to preterm delivery and their peers. Third, in contrast, women who have an SGA delivery exhibit neither an adverse pregravid cardiovascular risk factor profile nor evidence of the evolution thereof in the years before pregnancy. It thus emerges that an adverse cardiovascular risk factor profile evolves over time in the years before pregnancy complicated by preterm delivery but does not necessarily precede SGA.

There have been few previous studies of pregravid cardiovascular risk factors in women who subsequently experience preterm delivery.[16–18] These studies have been limited by modest numbers of cases with pregravid measurement of risk factors at a single point in time at 4 to 7 years before pregnancy. Using data from the Nord-Trøndelag Health study, Magnusson and colleagues reported that nonfasting bloodwork at ≈4 years before pregnancy showed higher levels of triglycerides, total cholesterol, and glucose, along with lower HDL cholesterol, in 272 women who went on to have preterm delivery.In the Coronary Artery Risk Development in Young Adults Study, both lower and higher total cholesterol measured at ≈6 years before pregnancy were noted in 218 women with self-reported preterm delivery.[17] In the Cardiovascular Risk in Young Finns Study, neither lipids nor glucose at median 7.4 years before pregnancy were significantly different between 67 women who subsequently had preterm delivery and those who did not.[18] The current study thus reconciles these conflicting observations with a much larger cohort of 156 278 women (including 11 078 with preterm delivery) in whom pregravid cardiovascular risk factors were measured on at least 2 occasions at median 0.6 and 1.9 years, respectively, before a first pregnancy. The resultant findings provide a definitive assessment of the pregravid cardiovascular risk factor profile of women who go on to have preterm delivery.

The findings illustrate several key elements of this profile. First, we demonstrate that there are consistent and sustained differences in glycemia, lipids, and ALT between women who go on to develop preterm delivery and those who do not. Second, these differences are not dependent on pre-eclampsia, which itself is associated with both preterm delivery and future risk of CVD (Table S2). Third, the differences in triglycerides, A1c, fasting glucose, and ALT are driven by divergent trajectories of these risk factors in the years before pregnancy between women who go on to preterm delivery and their peers. While differences in the annual rates of change may be modest in magnitude, the resultant divergent trajectories will cause initially modest differences to increase over time. By the time of the pregravid measurements shown in Table 2, all glycemic and lipid markers were worse in women who went on to preterm delivery than in their peers. Although the absolute levels of these glycemic and lipid markers would not warrant clinical intervention in young nulliparous women in practice, the distinct pregravid trajectories shown in Figure suggest that, over time, women who develop preterm delivery will face comparatively greater cumulative exposure to these vascular risk factors than their peers. This cumulative exposure potentially may contribute to their higher lifetime risk of CVD. Thus, the model emerging from these data posits that modest differences in cardiovascular risk factors that predate pregnancy in young adulthood gradually increase over time and ultimately contribute to the development of CVD. Indeed, this model has similarly emerged as a basis for the elevated lifetime risk of vascular disease in women with a history of gestational diabetes mellitus.[23]

Like preterm delivery and gestational diabetes mellitus, delivery of an SGA neonate is an adverse pregnancy outcome that predicts future maternal risk of CVD.[1,7] However, the current study suggests that the pregravid component of the cumulative exposure

model noted above may not apply to women with a history of SGA. Notably, in stark contrast to women with preterm delivery, the pregravid cardiovascular risk factors of women who go on to SGA are neither worse than that of their peers nor evolving along distinct trajectories. Moreover, when women are stratified according to both preterm and SGA delivery status, it is apparent that those with SGA alone have a comparatively favorable cardiovascular risk factor profile before pregnancy (Table S5). While the design of the current study precludes direct linkage of pregravid glycemic and lipid measures to future risk of CVD, our findings suggest that these relationships may be different between women with preterm delivery and those who deliver an SGA neonate. Although the mechanistic basis for our findings cannot be ascertained with these data, one possibility is that an adverse underlying cardiovascular risk factor profile may predispose women to preterm delivery and future CVD but does not predispose women to delivering an SGA neonate.

A strength of this study is the application of real-world data with multiple measurements of cardiovascular risk factors over time. Moreover, the sample size of 156 278 women (including 11 078 with preterm delivery and 19 367 with SGA) provides robust estimates. Although the performance of the laboratory tests in clinical care meant that all were not done at the same time, the presence of multiple pregravid measurements made it possible to study changes over time in these risk factors. A limitation is that there could be differences in comorbidities between the women with and without a sufficient number of laboratory tests to be included in the analytic sample, which may be related to clinical indications for performing laboratory tests. Indeed, the higher rates of hypertension and dyslipidemia in the women with 2 or more tests prompted the sensitivity analyses in which women with these diagnoses were excluded. Similarly, a recent study from the Better Outcomes Registry & Network noted a 6.1% prevalence of preterm birth in nulliparous women in Ontario,[24] which was slightly lower than our prevalence of 7.08%, and a 2009 report from the Canadian Institutes of Health Information reported an 8.9% prevalence of SGA in Ontario,[25] which is lower than our prevalence of 12.4%. These differences are not necessarily surprising when one considers that our sample was restricted to women who had 2 or more laboratory measurements of the indicated analytes before pregnancy. Thus, the possibility persists that unrecognized differences between the women with and without a sufficient number of tests could cause selection bias and limit the generalizability of our findings. Another limitation of the study is the lack of data on covariates such as smoking, blood pressure, and body mass index, which are not captured with the administrative data sources. In addition, dyslipidemia and hypertension were defined based on diagnostic coding recorded on physician service and hospitalization records, rather than on actual lipid and blood pressure levels. Therefore, while their specificity is likely high, their sensitivity may be suboptimal.

The findings from this study hold potential future implications for research and practice. First, these data suggest that higher glycemic and lipid measures in young nulliparous women potentially may enable pregravid identification of those who will be at greater risk of preterm delivery when they are pregnant. While current guidelines do not recommend these laboratory measurements in healthy young women before pregnancy, this possibility warrants further study. In particular, the finding of rising triglycerides over time may be relevant for such identification, in light of the 7.9-fold higher annual rate of change in this lipid measure in women who went on to preterm delivery. Second, the fact that an adverse risk factor profile precedes pregnancies complicated by preterm delivery suggests these factors may warrant closer postpartum surveillance in this patient population. Such surveillance and early intervention could raise the possibility of modifying the life course trajectories of these risk factors towards the ultimate goal of primary prevention of CVD. Of note, this approach would align with the concept of individualized postpartum care to improve long-term health in women, as recently suggested by the American College of Obstetrics and Gynecology.[26,27]

In summary, even before pregnancy, the cardiovascular risk factor profile of women who develop preterm delivery is distinct from that of their peers. Specifically, affected women have higher pregravid A1c, fasting glucose, random glucose, total cholesterol, LDL cholesterol, triglycerides, and ALT than their peers, coupled with lower HDL cholesterol. These differences arise because of distinct pregravid trajectories. In contrast, women who have an SGA delivery exhibit neither an adverse pregravid cardiovascular risk factor profile nor evidence of the evolution thereof in the years before pregnancy. It thus emerges that, although both diagnoses identify women at risk of future CVD, the early-life evolution of this later-life cardiovascular risk may differ between women with preterm delivery and those with SGA.

ARTICLE INFORMATION

Received February 17, 2021; accepted April 14, 2021.

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Acknowledgments

ICES is a nonprofit research institute funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of this material are based on data and/or information compiled and provided by Canadian Institute for Health Information (CIHI). The opinions, results, and conclusions reported in this study are those of the authors and are independent from the funding sources. No endorsement by ICES, the MOHLTC, or CIHI is intended or should be inferred. Shah is guarantor, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: Retnakaran conceived the hypothesis and wrote the manuscript. Retnakaran and Shah designed the analysis plan. Both authors interpreted the data and critically revised the manuscript for important intellectual content. Both authors approved the final manuscript.

Sources of Funding

This study was supported by Intramural Funds. Retnakaran holds the Boehringer Ingelheim Chair in Beta-cell Preservation, Function and Regeneration at Mount Sinai Hospital and his research program is supported by the Sun Life Financial Program to Prevent Diabetes in Women.

Disclosures

None.

Supplementary Material

Tables S1–S5
Figures S1–S2

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Supplemental Material

Table S1. Sample size for each analyte.

Analyte	Sample size
A1c	42,588
Fasting glucose	50,170
Random glucose	91,869
Total cholesterol	69,837
LDL cholesterol	68,168
HDL cholesterol	68,433
Triglycerides	69,304
ALT	114,998
AST	37,517

Table S2. Mean adjusted values of pregravid cardiometabolic risk factors in (i) women with and without preterm delivery and (ii) women with and without SGA delivery, after adjustment for age, ethnicity, income, rurality and pre-eclampsia.

	Not Preterm	Preterm	P	Not SGA	SGA	P
A1c (%)						
Measurement before pregnancy:	5.31 ± 0.002	5.36 ± 0.006	<0.0001	5.31 ± 0.002	5.32 ± 0.004	0.24
Preceding measurement:	5.35 ± 0.005	5.39 ± 0.007	<0.0001	5.35 ± 0.005	5.36 ± 0.006	0.30
Fasting glucose (mmol/l)						
Measurement before pregnancy:	4.73 ± 0.002	4.75 ± 0.008	0.0005	4.73 ± 0.002	4.69 ± 0.006	<0.0001
Preceding measurement:	4.69 ± 0.007	4.70 ± 0.010	0.17	4.70 ± 0.007	4.65 ± 0.009	<0.0001
Random glucose (mmol/l)						
Measurement before pregnancy:	4.88 ± 0.003	4.93 ± 0.010	<0.0001	4.89 ± 0.003	4.86 ± 0.008	0.0002
Preceding measurement:	4.84 ± 0.009	4.89 ± 0.013	<0.0001	4.85 ± 0.009	4.81 ± 0.011	<0.0001
Total cholesterol (mmol/l)						
Measurement before pregnancy:	4.55 ± 0.004	4.64 ± 0.012	<0.0001	4.56 ± 0.004	4.54 ± 0.009	0.01
Preceding measurement:	4.55 ± 0.010	4.64 ± 0.015	<0.0001	4.56 ± 0.010	4.53 ± 0.013	0.01
LDL cholesterol (mmol/l)						
Measurement before pregnancy:	2.52 ± 0.003	2.59 ± 0.011	<0.0001	2.53 ± 0.003	2.51 ± 0.008	0.02
Preceding measurement:	2.54 ± 0.009	2.62 ± 0.014	<0.0001	2.55 ± 0.009	2.53 ± 0.012	0.05
HDL cholesterol (mmol/l)						
Measurement before pregnancy:	1.57 ± 0.002	1.54 ± 0.006	<0.0001	1.57 ± 0.002	1.58 ± 0.004	0.005
Preceding measurement:	1.55 ± 0.005	1.52 ± 0.007	<0.0001	1.55 ± 0.005	1.56 ± 0.006	0.02
Triglycerides (mmol/l)						
Measurement before pregnancy:	1.01 ± 0.003	1.11 ± 0.009	<0.0001	1.02 ± 0.003	0.99 ± 0.007	<0.0001
Preceding measurement:	1.01 ± 0.007	1.10 ± 0.011	<0.0001	1.02 ± 0.007	0.98 ± 0.010	<0.0001
ALT (IU/L)						
Measurement before pregnancy:	18.8 ± 0.1	20.1 ± 0.2	<0.0001	18.9 ± 0.1	18.5 ± 0.2	0.01
Preceding measurement:	19.7 ± 0.3	21.1 ± 0.4	<0.0001	19.8 ± 0.3	19.2 ± 0.3	0.008

Table S3. Mean adjusted values of pregravid cardiometabolic risk factors in (i) women with and without preterm delivery and (ii) women with and without SGA delivery, after excluding those with hypertension, and adjusted for age, ethnicity, income, and

	Not Preterm	Preterm	P	Not SGA	SGA	P
A1c (%)						
Measurement before pregnancy:	5.30 ± 0.002	5.36 ± 0.006	<0.0001	5.31 ± 0.002	5.31 ± 0.004	0.17
Preceding measurement:	5.34 ± 0.002	5.38 ± 0.006	<0.0001	5.34 ± 0.002	5.35 ± 0.004	0.24
Fasting glucose (mmol/l)						
Measurement before pregnancy:	4.72 ± 0.002	4.75 ± 0.008	0.0005	4.73 ± 0.002	4.68 ± 0.006	<0.0001
Preceding measurement:	4.70 ± 0.002	4.71 ± 0.008	0.12	4.70 ± 0.002	4.65 ± 0.006	<0.0001
Random glucose (mmol/l)						
Measurement before pregnancy:	4.88 ± 0.003	4.93 ± 0.010	<0.0001	4.88 ± 0.003	4.85 ± 0.008	0.0004
Preceding measurement:	4.84 ± 0.003	4.89 ± 0.010	<0.0001	4.85 ± 0.003	4.81 ± 0.008	<0.0001
Total cholesterol (mmol/l)						
Measurement before pregnancy:	4.50 ± 0.004	4.59 ± 0.012	<0.0001	4.55 ± 0.004	4.53 ± 0.009	0.007
Preceding measurement:	4.50 ± 0.004	4.60 ± 0.012	<0.0001	4.56 ± 0.004	4.53 ± 0.009	0.007
LDL cholesterol (mmol/l)						
Measurement before pregnancy:	2.47 ± 0.003	2.55 ± 0.010	<0.0001	2.52 ± 0.003	2.50 ± 0.008	0.01
Preceding measurement:	2.50 ± 0.003	2.58 ± 0.010	<0.0001	2.54 ± 0.003	2.52 ± 0.008	0.04
HDL cholesterol (mmol/l)						
Measurement before pregnancy:	1.58 ± 0.002	1.54 ± 0.006	<0.0001	1.57 ± 0.002	1.58 ± 0.004	0.02
Preceding measurement:	1.56 ± 0.002	1.53 ± 0.006	<0.0001	1.56 ± 0.002	1.56 ± 0.004	0.05
Triglycerides (mmol/l)						
Measurement before pregnancy:	0.99 ± 0.003	1.10 ± 0.008	<0.0001	1.02 ± 0.003	0.98 ± 0.007	<0.0001
Preceding measurement:	1.00 ± 0.003	1.10 ± 0.008	<0.0001	1.03 ± 0.003	0.98 ± 0.007	<0.0001
ALT (IU/L)						
Measurement before pregnancy:	21.7 ± 0.1	22.6 ± 0.4	0.01	18.8 ± 0.1	18.4 ± 0.2	0.04
Preceding measurement:	23.7 ± 0.2	24.0 ± 0.6	0.61	19.7 ± 0.1	19.1 ± 0.2	0.02

Table S4. Mean adjusted values of pregravid cardiometabolic risk factors in (i) women with and without preterm delivery and (ii) women with and without SGA delivery, after excluding those with dyslipidemia, and adjusted for age, ethnicity, income, and

	Not Preterm	Preterm	P	Not SGA	SGA	P
A1c (%)						
Measurement before pregnancy:	5.30 ± 0.002	5.36 ± 0.006	<0.0001	5.31 ± 0.002	5.31 ± 0.004	0.11
Preceding measurement:	5.34 ± 0.002	5.38 ± 0.006	<0.0001	5.34 ± 0.002	5.35 ± 0.004	0.17
Fasting glucose (mmol/l)						
Measurement before pregnancy:	4.72 ± 0.002	4.75 ± 0.008	<0.0001	4.73 ± 0.002	4.68 ± 0.006	<0.0001
Preceding measurement:	4.70 ± 0.002	4.71 ± 0.008	0.10	4.70 ± 0.003	4.65 ± 0.006	<0.0001
Random glucose (mmol/l)						
Measurement before pregnancy:	4.88 ± 0.003	4.93 ± 0.010	<0.0001	4.89 ± 0.003	4.86 ± 0.008	0.004
Preceding measurement:	4.84 ± 0.003	4.89 ± 0.010	<0.0001	4.85 ± 0.003	4.82 ± 0.008	<0.0001
Total cholesterol (mmol/l)						
Measurement before pregnancy:	4.54 ± 0.004	4.64 ± 0.012	<0.0001	4.51 ± 0.004	4.49 ± 0.009	0.049
Preceding measurement:	4.55 ± 0.004	4.64 ± 0.012	<0.0001	4.51 ± 0.004	4.49 ± 0.009	0.047
LDL cholesterol (mmol/l)						
Measurement before pregnancy:	2.52 ± 0.003	2.59 ± 0.011	<0.0001	2.48 ± 0.003	2.47 ± 0.008	0.049
Preceding measurement:	2.53 ± 0.003	2.62 ± 0.011	<0.0001	2.50 ± 0.003	2.48 ± 0.008	0.14
HDL cholesterol (mmol/l)						
Measurement before pregnancy:	1.58 ± 0.002	1.54 ± 0.006	<0.0001	1.57 ± 0.002	1.58 ± 0.004	0.02
Preceding measurement:	1.56 ± 0.002	1.52 ± 0.006	<0.0001	1.56 ± 0.002	1.57 ± 0.004	0.10
Triglycerides (mmol/l)						
Measurement before pregnancy:	1.00 ± 0.003	1.11 ± 0.009	<0.0001	1.00 ± 0.003	0.98 ± 0.006	<0.0001
Preceding measurement:	1.01 ± 0.003	1.11 ± 0.009	<0.0001	1.01 ± 0.003	0.98 ± 0.006	<0.0001
ALT (IU/L)						
Measurement before pregnancy:	18.7 ± 0.1	20.1 ± 0.2	<0.0001	18.9 ± 0.1	18.5 ± 0.2	0.03
Preceding measurement:	19.5 ± 0.1	21.0 ± 0.3	<0.0001	19.7 ± 0.1	19.2 ± 0.2	0.03

Table S5. Mean adjusted values of pregravid cardiometabolic risk factors in study population stratified into 4 groups based on presence or absence of SGA and preterm delivery (PTD), respectively. Values are adjusted for age, ethnicity, income and rurality.

		SGA Only (n=17,670)		Neither SGA nor PTD (n=127,503)		SGA and PTD (n=1,697)		PTD Only (n=9,285)		
Analyte	**Timing**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**P**
A1c (%)	Measurement before pregnancy	5.31	0.002	5.31	0.002	5.38	0.014	5.36	0.006	<.0001
	Preceding measurement	5.35	0.005	5.35	0.005	5.41	0.014	5.39	0.008	<.0001
Fasting gluc (mmol/l)	Measurement before pregnancy	4.73	0.002	4.73	0.002	4.70	0.019	4.77	0.008	<.0001
	Preceding measurement	4.69	0.007	4.69	0.007	4.68	0.020	4.71	0.011	<.0001
Random gluc (mmol/l)	Measurement before pregnancy	4.88	0.003	4.88	0.003	4.97	0.024	4.93	0.011	<.0001
	Preceding measurement	4.85	0.009	4.85	0.010	4.89	0.025	4.89	0.013	<.0001
Total chol (mmol)	Measurement before pregnancy	4.55	0.004	4.55	0.004	4.63	0.029	4.65	0.013	<.0001
	Preceding measurement	4.55	0.010	4.55	0.010	4.60	0.031	4.65	0.016	<.0001
LDL chol (mmol/l)	Measurement before pregnancy	2.52	0.003	2.52	0.003	2.59	0.026	2.61	0.011	<.0001
	Preceding measurement	2.54	0.009	2.54	0.009	2.59	0.028	2.63	0.014	<.0001
HDL chol (mmol/l)	Measurement before pregnancy	1.57	0.002	1.57	0.002	1.55	0.014	1.53	0.006	<.0001
	Preceding measurement	1.55	0.005	1.55	0.005	1.52	0.014	1.51	0.007	<.0001
Triglycerides (mmol/l)	Measurement before pregnancy	1.02	0.003	1.02	0.003	1.08	0.022	1.13	0.009	<.0001
	Preceding measurement	1.01	0.007	1.01	0.007	1.07	0.023	1.12	0.012	<.0001
ALT (IU/L)	Measurement before pregnancy	18.8	0.076	18.8	0.077	19.6	0.585	20.3	0.254	<.0001
	Preceding measurement	19.7	0.256	19.7	0.292	20.5	0.791	21.3	0.404	<.0001

Figure S1. Derivation of study population.

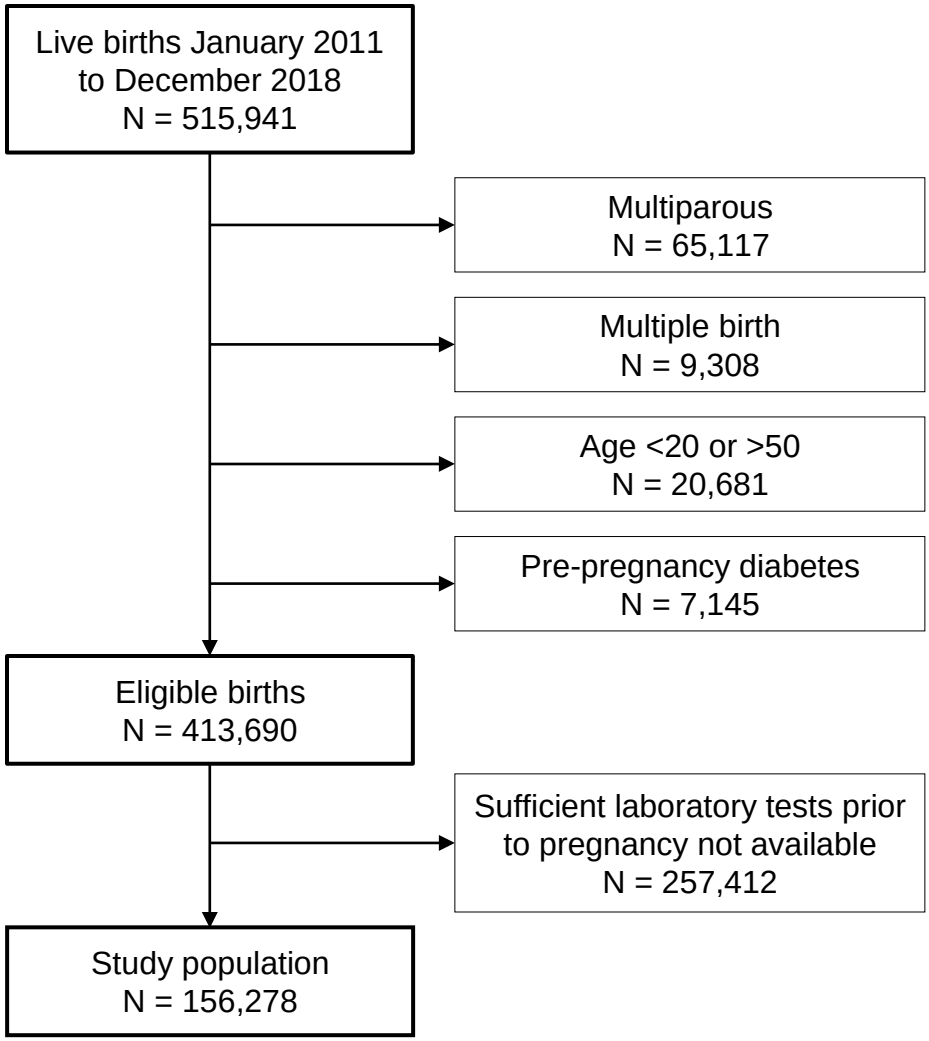

Figure S2. Predicted trajectories of the following cardiovascular risk factors in the years before pregnancy in a 30.6-year-old woman from the general population and the middle income quintile who goes on to have SGA delivery and one who does not: (A) A1c, (B) fasting glucose, (C) random glucose, (D) total cholesterol, (E) LDL cholesterol, (F) HDL cholesterol, (G) triglycerides, and (H) ALT.