

Caucasian and Asian difference in role of type 1 diabetes on large-for-gestational-age neonates

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ABSTRACT

Introduction Racial differences in the association between type 1 diabetes mellitus (T1DM) and large-for-gestational-age (LGA) neonates remain unclear. The objective of this study was to compare the effect of T1DM on LGA neonates between Caucasian and Asian women.

Research design and methods A population-based retrospective cohort study was conducted among Caucasian and Asian women who had prenatal screening and gave a singleton live birth in an Ontario hospital between April 2015 and March 2018. Multivariable log-binomial regression models were used to estimate the adjusted relative risks (aRRs) and 95% CIs of T1DM on LGA for Caucasian and Asian women. Relative contribution of T1DM to LGA was examined by multivariable logistic regression model, stratified by Caucasian and Asian women.

Results A total of 232 503 women (69.4% Caucasians and 30.6% Asians) were included in the final analysis. The rate of T1DM was higher in Caucasians (0.5%) than in Asians (0.2%), and the rate of LGA neonates was also higher in Caucasians (11.0%) than in Asians (5.0%). The association between T1DM and LGA in Caucasians (aRR 4.18, 95% CI (3.84 to 4.55)) was more robust than that in Asians (aRR 2.11, 95% CI (1.24 to 3.59)). T1DM was the fourth strongest contributor to LGA in Caucasians, while T1DM was the seventh contributor to LGA in Asians.

Conclusions T1DM plays a more substantial role in LGA among Caucasians than Asians. Clinicians should be aware of the Caucasian–Asian differences of effects of T1DM on LGA when developing pregnancy management strategies.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by selective destruction of the insulin-secreting β cells, making up an estimated 5%–10% of all diabetes cases.¹ It is well recognized that women with T1DM have two to five times higher risk of large-for-gestational-age (LGA) neonates, resulting in short-term and long-term adverse maternal and offspring outcomes. The short-term complications include prolonged labor, third-degree and fourth-degree perineal tears, postpartum hemorrhage, and cesarean section, neonatal hypoglycemia, respiratory disorders, hyperbilirubinemia, shoulder

Significance of this study

What is already known about this subject?

- Incidence of type 1 diabetes mellitus (T1DM) is substantially higher among Caucasians than Asians.
- Maternal prepregnancy obesity, excessive gestational weight gain, and gestational diabetes are well-documented risk factors for large-for-gestational age (LGA) across different race groups, but the racial differences in the association between T1DM and LGA remain unclear.

What are the new findings?

- Rates of T1DM and LGA were higher in Caucasians than in Asians.
- Significant modification effect of race on the association between T1DM and LGA was observed, with stronger association of T1DM with LGA in Caucasians than in Asians.
- T1DM was the fourth strongest contributor to LGA in Caucasians, while it was the seventh contributor to LGA development in Asians.

How might these results change the focus of research or clinical practice?

- Further research on better understanding the etiology of Caucasian–Asian differences in effect of T1DM on LGA would be of value to inform clinical practices on prenatal management to possibly prevent T1DM-associated morbidity in the offspring.

dystocia, and admission to the neonatal intensive care unit.^{2–4} In addition, infants with LGA have an increased lifetime risk of obesity, type 2 diabetes mellitus (T2DM), and chronic diseases.⁵

The incidence of T1DM has been increasing by 2%–5% worldwide in the past decade, with approximately 78 000 youth newly diagnosed annually.^{6,7} In the USA, the number of people affected by T1DM is estimated to be up to three million.⁷ In Canada, about 300 000 Canadians live with T1DM, and the annual incidence rate has been growing at an estimated 5.1% which is higher than the global average.⁸ It has been reported that there were

significant racial differences in the incidence of T1DM between Caucasians and Asians below the age of 15 years old, with a high incidence rate above 20 cases per 100 000 per year in Caucasians, while a rate of less than 1 case per 100 000 individuals per year has been reported in some Asian countries.⁹

Appropriate glycemic control before and during pregnancy is believed to be the basis for improved pregnancy outcome among women affected by T1DM. Unfortunately, the rate of fetal overgrowth remains significant at around 50% among pregnancies with T1DM, even though many advances in diabetes management and therapies have been applied,¹⁰ suggesting that other contributors may be involved. In addition to T1DM, maternal prepregnancy obesity, excessive gestational weight gain, gestational diabetes, and T2DM are known as the main risk factors of LGA.^{11 12} Several studies showed racial differences in effects of prepregnancy obesity, gestational weight gain, and gestational diabetes on LGA,^{13 14} but the Caucasian–Asian disparities in the association between T1DM and LGA were not reported.

The mechanisms of Caucasian–Asian differences in T1DM remain unclear. Clinical and immunologic characteristics of T1DM in Asian populations are different from those of Caucasians.⁹ Furthermore, the underlying pathophysiology of T1DM in pregnancy and risk of LGA neonates between Caucasians and Asians might be fundamentally different due to differences in genetic and environmental factors.⁶ Some investigators have suggested that the immune attack at insulin-secreting beta cells as the pathogenesis of T1DM may involve polygenic factors and environmental triggers.¹⁵ The primary genetic susceptibility of T1DM has been reported to be attributable to the high-risk human leukocyte antigen (HLA) genotypes and haplotypes, which present less frequently in Asians.⁹ It potentially leads to less severe T-cell-mediated immune destruction of beta cells in the pancreatic islets of Langerhans in Asians than in Caucasians, with lower level of islet-specific autoantibodies.⁹ Racial differences in dietary protein intake, gut microbiota, chemical toxin exposure,^{16–18} and viral or bacterial infections¹⁵ may also lead to heterogeneous autoimmune pathways in destroying beta cells between Caucasians and Asians. Thus, it is reasonable to assume that the role of T1DM on LGA may be different between Caucasians and Asians.

The current study aims to examine the Caucasian–Asian differences in the association between T1DM and LGA neonates, including the relative contribution of T1DM to neonatal LGA in Ontario, the most populous province with a high concentration of Asian population in Canada.

RESEARCH DESIGN AND METHODS

Study design and data sources

The study design is a population-based retrospective cohort. We use data obtained from the Better Outcomes

Registry & Network (BORN) Ontario birth registry (<https://www.bornontario.ca/en/about-born/>), the largest and most robust perinatal dataset in Canada. The BORN registry contains maternal race and clinical data related to pregnancy and birth, including T1DM, T2DM, gestational diabetes, body mass index (BMI, weight in kilogram divided by height in meter squared), gestational weight gain, gestational age, and birth weight. Furthermore, to increase the identification of T1DM, T2DM, gestational diabetes cases, BORN records were linked to correspondence national Discharge Abstract Database (DAD), administered by the Canadian Institute for Health Information (CIHI) through healthcare number, for which BORN has a copy.¹⁹

Study population

The study population included Caucasian and Asian women who had prenatal screening and resulted in a live singleton birth in an Ontario hospital between April 2015 and March 2018. Approximately 70% of Ontario pregnant women received prenatal screening in 2016. We excluded pregnant women with any of the following conditions: maternal race other than Asian and Caucasian, missing data of infant birth weight, gestational age at birth less than 22 weeks or greater than 42 weeks, multi-fetal pregnancies, pregnancies with a fetal congenital anomaly diagnosis, and a second gestation (for women who had two births in the study years).

Outcome measure

The outcome of interest is LGA neonates, which was defined as birth weight greater than 90th percentile according to sex-specific Canadian birth weight reference for singletons.²⁰

Exposure measures

T1DM is the main exposure of interest. T1DM was primarily identified by a variable of “diabetes during pregnancy” which captures diagnosis of T1DM in BORN registry data. In addition, we linked BORN data to CIHI-DAD data to improve the ascertainment of T1DM by using maternal diagnosis codes (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada, E10). The diagnosis of diabetes in Ontario is based on the Diabetes Canada Clinical Practice Guidelines: fasting plasma glucose ≥ 7.0 mmol/L or glycated hemoglobin $\geq 6.5\%$ or 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥ 11.1 mmol/L or random plasma glucose ≥ 11.1 mmol/L.²¹ Individuals with T1DM is likely younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia. The autoantibody test will be used to differentiate between T1DM and T2DM.²¹

Covariates

Covariates and confounders considered in this study were based on literature report and data availability, and included T2DM (yes or no), gestational diabetes (yes or no), prepregnancy BMI (< 25 or ≥ 25 kg/m²), gestational

weight gain categories (inadequate, within recommended, and excessive according to Institute of Medicine recommendation),²² maternal age at birth (<35 or ≥35 years), parity (nulliparous or multiparous), social drug use/alcohol consumption/cigarette smoking during pregnancy (yes or no), conceived by assisted reproductive technology (yes or no), maternal mental health issues including anxiety or depression (yes or no), and a composite variable of any pre-existing maternal physical health conditions including pre-existing hypertension, pre-existing heart disease or pulmonary disease (yes or no). Because there is no record of income in BORN, we calculated the neighborhood household median income quintile (lowest, second, third, fourth, highest) by linking 2011 Canadian Census data with maternal postal code, using Statistics Canada's Postal Code Conversion File Plus (PCCF+).²³

Effect modifier

Race is considered as the moderator/effect modifier for the association between T1DM and risk of LGA. The eligible women comprise two racial groups in our study: Caucasian and Asian. Maternal race was self-reported by women and recorded by the prenatal care provider who completed the prenatal screening requisition.

Statistical analysis

We described maternal demographic characteristics and clinical factors, stratified by Caucasians and Asians. Categorical variables were described by count and per cent, and continuous variables were described by mean and SD. Rates of T1DM and LGA were compared between Caucasians and Asians. We assessed the associations between covariates and maternal race using Student's t-test for continuous data, and χ^2 tests for categorical data.

Prior to testing the Caucasian–Asian differences in association between T1DM and LGA, we assessed the modification effect of race on the association between T1DM and LGA using Wald test. As the significant modification effect of race was detected, we primarily reported the racial-specific effect of T1DM using stratified regression analysis. Multivariable log-binomial regression models were used to estimate the adjusted relative risk (aRR) with 95% CI of T1DM on LGA, stratified by Caucasians and Asians. Since the stratified approach does not provide a test of statistical significance of the difference between the stratified RRs, we further included the interaction term of *race*T1DM* in one regression model to examine the racial-specific effect by using a specified level approach.²⁴

Other factors associated with LGA including excessive gestational weight gain, T2DM, gestational diabetes, high BMI, advanced maternal age, parity, smoking, anxiety or depression, and conception with assisted reproductive technology, and pre-existing health conditions were also examined. In addition to those relevant factors, we considered a series of covariates to be potential confounders including neighborhood household median income,

social drug use/alcohol consumption during pregnancy, antenatal healthcare provider and maternal hospital level of care. Confounders were identified by statistically significant and clinically relevant associations with exposure and outcome in univariate regression analysis. When conducting the adjusted regression model, if one independent variable will be treated as main exposure, other variables will be treated as covariates/confounders. Multiple imputation methods were used to account for missing data on the following covariates: maternal age at delivery (0.1% missing), neighborhood household income (5.1% missing), parity (1.3% missing), prepregnancy BMI (14.1% missing), gestational weight gain (14.1% missing), and conception type (6.8%). Ten datasets were imputed by using the fully condition specification logistic regression method. All regression analyses were performed after missing data multiple imputations.

To estimate the relative contribution of each risk factor to LGA, we further used multivariable logistic regression models to calculate the standardized coefficient, stratified by Caucasians and Asians. In addition to T1DM, the contributions of other common risk factors were compared between Caucasian and Asian women, including gestational weight gain, high BMI, T2DM, parity, gestational diabetes, advanced maternal age, and conception with assisted reproductive technology. The absolute value of standardized regression coefficient reflected the contribution of each predictor to LGA neonates.

Sensitivity analysis

Two sensitivity analyses were conducted to examine the robustness of our main results. First, we used racial-specific birthweight curves to identify LGA neonates²⁵ and evaluate the Caucasian–Asian differences in effect of T1DM on LGA. Second, we performed the completed cases analysis to compare the results with those obtained from missing data imputed database.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, V.9.4 (SAS Institute, Cary, North Carolina, USA), with two-tailed tests and a significance level of $p < 0.05$.

RESULTS

A total of 232 503 eligible women were included in the final analysis. Among them, 69.4% were Caucasian women and 30.6% were Asian women.

Maternal demographic and clinical characteristics stratified by Caucasian and Asian are shown in [table 1](#). The prevalence of T1DM was higher in Caucasian (0.5%) than that in Asian women (0.2%) ($p < 0.001$). The prevalence of LGA neonates was higher in Caucasian (11.0%) than that in Asian women (5.0%) ($p < 0.001$). Compared with Caucasian women, Asian women were more likely to have child at older age and with lower family income. Asian women were less likely to be obese, have excessive

Table 1 Characteristics of women who were eligible for the study, stratified by Caucasian and Asian women

Characteristics	Caucasian (n=1 61 251)		Asian (n=71 252)		Total (N=2 32 503)		P value
	n	%	n	%	N	%	
Large-for-gestational-age neonates	17 852	11.1	3566	5.0	21 418	9.2	<0.001
Type 1 diabetes	798	0.5	165	0.2	963	0.4	<0.001
Maternal age at delivery (years) (mean±SD)	31.0±5.1		32.0±4.5				
≤19	2641	1.6	135	0.2	2776	1.2	<0.001
20–34	118 818	73.7	50 423	70.8	169 241	72.8	
35–39	33 216	20.6	17 046	23.9	50 262	21.6	
≥40	6439	4.0	3598	5.0	10 037	4.3	
Missing	137	0.1	50	0.1	187	0.1	
Neighborhood median family income quintiles							
Quintile 1 (lowest)	26 963	16.7	16 123	22.6	43 086	18.5	<0.001
Quintile 2	26 637	16.5	11 093	15.6	37 730	16.2	
Quintile 3	29 476	18.3	12 828	18.0	42 304	18.2	
Quintile 4	38 886	24.1	16 779	23.5	55 665	23.9	
Quintile 5 (highest)	31 415	19.5	10 533	14.8	41 948	18.0	
Missing	7874	4.9	3896	5.5	11 770	5.1	
Parity							
0	75 205	46.6	30 085	42.2	105 290	45.3	<0.001
≥1	84 143	52.2	39 946	56.1	124 089	53.4	
Missing	1903	1.2	1221	1.7	3124	1.3	
Body mass index (BMI) (kg/m ²) (mean±SD)	26.2±6.2		24.0±4.6				
Underweight (BMI <18.5)	4091	2.5	3704	5.2	7795	3.4	<0.001
Normal (BMI 18.5–24.9)	69 316	43.0	34 196	48.0	103 512	44.5	
Overweight (BMI 25.0–29.9)	37 757	23.4	14 082	19.8	51 839	22.3	
Obese (BMI ≥30)	30 955	19.2	5569	7.8	36 524	15.7	
Missing	19 132	11.9	13 701	19.2	32 833	14.1	
Gestational weight gain* (kg) (mean±SD)	13.6±10.9		12.0±9.6				
Less than recommended	40 390	25.0	22 396	31.4	62 786	27.0	<0.001
Within recommended range	30 442	18.9	15 596	21.9	46 038	19.8	
More than recommended	71 287	44.2	19 559	27.5	90 846	39.1	
Missing	19 132	11.9	13 701	19.2	32 833	14.1	
Conception type							
In vitro fertilization	3294	2.0	1250	1.8	4544	2.0	<0.001
Intrauterine insemination	3209	2.0	1108	1.6	4317	1.9	
Spontaneous conception	143 849	89.2	63 911	89.7	207 760	89.4	
Missing	10 899	6.8	4983	7.0	15 882	6.8	
Drug use during pregnancy†‡	2961	1.8	145	0.2	3106	1.3	<0.001
Alcohol exposure during pregnancy†‡	4366	2.7	587	0.8	4953	2.1	<0.001
Smoking during pregnancy (any time)§	16 719	10.4	745	1.0	17 464	7.5	<0.001
Pre-existing hypertension	1430	0.9	584	0.8	2014	0.9	0.1184
Pre-existing type 2 diabetes	713	0.4	651	0.9	1364	0.6	<0.001
Pre-existing heart disease	2287	1.4	327	0.5	2614	1.1	<0.001
Pulmonary disease	7501	4.7	802	1.1	8303	3.6	<0.001
Anxiety†¶	18 831	11.7	1189	1.7	20 020	8.6	<0.001

Continued

Table 1 Continued

Characteristics	Caucasian (n=1 61 251)		Asian (n=71 252)		Total (N=2 32 503)		P value
	n	%	n	%	N	%	
Depression ^{‡¶}	14 520	9.0	1 199	1.7	15 719	6.8	<0.001
Gestational diabetes	9 236	5.7	10 451	14.7	19 687	8.5	<0.001
Antenatal healthcare provider							
Inclusive of family physician	17 144	10.6	3 509	4.9	20 653	8.9	<0.001
Obstetrician	81 793	50.7	55 824	78.3	137 617	59.2	
Family physician+obstetrician	27 403	17.0	3 968	5.6	31 371	13.5	
Midwife	23 168	14.4	3 609	5.1	26 777	11.5	
None	184	0.1	91	0.1	275	0.1	
Other	1 987	1.2	300	0.4	2 287	1.0	
Missing/unknown	9 572	5.9	3 951	5.5	13 523	5.8	
Maternal hospital care of level**							
Level I	17 188	10.7	696	1.0	17 884	7.7	<0.001
Level IIa	17 485	10.8	2 450	3.4	19 935	8.6	
Level IIb	40 312	25.0	22 847	32.1	63 159	27.2	
Level IIc	41 975	26.0	32 782	46.0	74 757	32.2	
Level III	43 313	26.9	11 340	15.9	54 653	23.5	
Missing	978	0.6	1 137	1.6	2 115	0.9	
Baby gender							
Male	82 653	51.3	36 493	51.2	119 146	51.2	0.76
Female	78 598	48.7	34 759	48.8	113 357	48.8	

Missing data were included from the percentage calculation.

*2009 Institute of Medicine recommendations.

†Drug use, alcohol use constitute any drug or alcohol use during pregnancy.

‡Self-reported variables.

§Maternal smoking during pregnancy captures any smoking either at the first prenatal visit or at the time of labor/admission for delivery.

¶Anxiety or depression constitutes concerns during this pregnancy including those pre-existing, diagnosed during pregnancy, or active during pregnancy.

**Maternal hospital level of care classification based on newborn and maternal needs, risk and illness as defined by the Provincial Council for Maternal and Child Health (Ontario).

gestational weight gain, report smoking during pregnancy, and to have mental health issues.

Figure 1 illustrates the characteristics associated with LGA, stratified by Caucasian and Asian women. In Caucasian women, T1DM (aRR 4.18, 95% CI (3.84 to 4.55)), T2DM (aRR 1.99, 95% CI (1.76 to 2.25)), gestational diabetes (aRR 1.44, 95% CI (1.37 to 1.52)), high BMI (>25 kg/m²) (aRR 1.53, 95% CI (1.48 to 1.59)), excessive gestational weight gain (aRR 1.81, 95% CI (1.74 to 1.89)), multiparous (aRR 1.66, 95% CI (1.61 to 1.72)), anxiety or depression (aRR 1.06, 95% CI (1.02 to 1.1)), pre-existing health issues (aRR 1.01, 95% CI (0.96 to 1.05)), conception with assisted reproductive technology (aRR 1.14, 95% CI (1.06 to 1.22)) were identified significantly associated with increased risk of LGA neonates after adjustment for maternal demographic and clinical characteristics. However, in Asian women, T1DM (aRR 2.11, 95% CI (1.24 to 3.59)), T2DM (aRR 2.12, 95% CI (1.71 to 2.64)), gestational diabetes (aRR 1.34, 95% CI (1.22 to

1.47)), high BMI (>25 kg/m²) (aRR 1.57, 95% CI (1.45 to 1.71)), excessive gestational weight gain (aRR 2.86, 95% CI (2.58 to 3.16)), advanced maternal age (>35 years old) (aRR 1.24, 95% CI (1.14 to 1.34)), and multiparous (aRR 1.69, 95% CI (1.55 to 1.84)) were significantly associated with increased risk of LGA neonates (online supplemental table S1).

Table 2 shows, in overall, women with T1DM have an increased risk of LGA neonates (aRR 2.96, 95% CI (2.27 to 3.86)), compared with women without T1DM, after adjusting for maternal age, neighborhood income level, prepregnancy BMI, gestational weight gain, parity and conception type, smoking, pre-existing health conditions, and mental health issues. Moreover, there was a significant modification effect of race on the association between T1DM and LGA neonates (Wald p<0.01). The stratified regression approach (model 2) found that the association between T1DM and LGA neonates in Caucasian women (aRR 4.18, 95% CI (3.84 to 4.55))

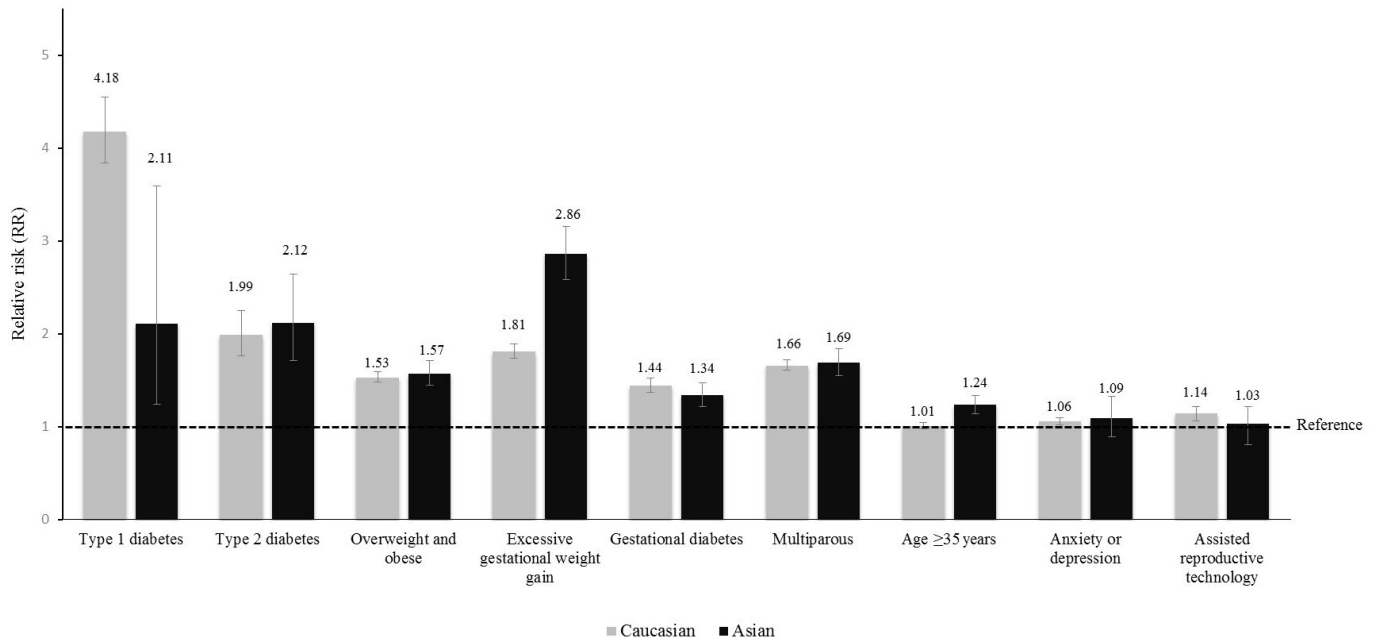


Figure 1 Relative risk of each risk factor on large-for-gestational-age neonates. Models were adjusted for maternal age, neighborhood income level, parity, smoking, prepregnancy body mass index, gestational weight gain, conception type, pre-existing maternal health conditions (including pre-existing hypertension, pre-existing heart disease, or pulmonary disease), type 2 diabetes, gestational diabetes, anxiety, and depression. If one independent variable will be treated as main exposure, other factors will be treated as covariates/confounders.

was stronger than that in Asian women (aRR 2.11, 95% CI (1.23 to 3.59)). When including the interaction term of *race*T1DM* in the regression model (model 3), we found consistent results (Caucasian: aRR 4.18, 95% CI (3.83 to 4.55); Asian: aRR 2.10, 95% CI (1.24 to 3.54)).

Figures 2 and 3 present the standardized coefficient of each risk factor for LGA neonates among Caucasian and Asian women. T1DM was the fourth strongest contributor (standardized coefficient: 0.08) of LGA neonates in Caucasian women, following excessive gestational

weight gain (standardized coefficient: 0.18), multiparous (standardized coefficient: 0.16), and high BMI (standardized coefficient: 0.13). However, T1DM was the seventh contributor of LGA in Asian women (standardized coefficient: 0.02), following excessive gestational weight gain (standardized coefficient: 0.25), multiparous (standardized coefficient: 0.15), high BMI (standardized coefficient: 0.13), gestational diabetes (standardized coefficient: 0.06), advanced maternal age (standardized

Table 2 Effect of T1DM on LGA neonates among Caucasian and Asian women

	LGA neonates				Adjusted RR (95% CI)*†
	T1DM (yes)		T1DM (no)		
	n	%	n	%	
Model 1: Main effect of T1DM in whole study population	435	45.2	20983	9.1	2.96 (2.27 to 3.86)
Model 2: Stratified regression approach					
Effect of T1DM among Caucasian women	314	52	14250	11	4.18 (3.84 to 4.55)
Effect of T1DM among Asian women	13	14.1	2594	5.1	2.11 (1.24 to 3.59)
Model 3: Specified levels approach with interaction term in the model					
Effect of T1DM among Caucasian women	314	52.2	14250	11.1	4.18 (3.83 to 4.55)
Effect of T1DM among Asian women	13	14.1	2594	5.1	2.10 (1.24 to 3.54)

*Adjusted for covariates: maternal age, neighborhood income level, parity, smoking, prepregnancy BMI, gestational weight gain, conception type, pre-existing maternal health conditions (including pre-existing hypertension, pre-existing heart disease, or pulmonary disease), type 2 diabetes, gestational diabetes, anxiety, and depression.

†Multivariable log-binomial regression models were used to estimate the relative risks. Missing values of maternal age, median household income, parity and prepregnancy BMI, gestational weight gain and conception type were imputed by fully conditional specification logistic regression (a generalized logit distribution) method.

BMI, body mass index; LGA, large-for-gestational age; RR, relative risk; T1DM, type 1 diabetes mellitus.

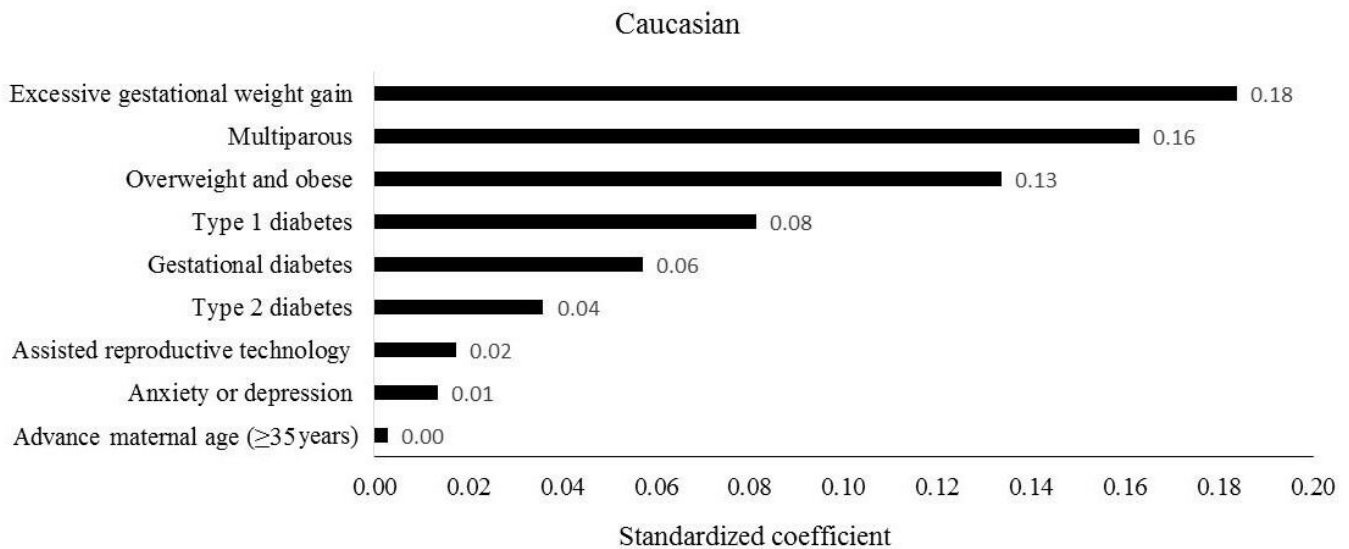


Figure 2 Contribution (standard coefficient) of each risk factor to large-for-gestational-age neonates among Caucasian women.

coefficient: 0.06), and T2DM (standardized coefficient: 0.05).

Sensitivity analyses found similar results with completed case analysis (online supplemental table S2). When using racial-specific birth weight reference to identify LGA neonates, the significant effect of T1DM on LGA in Asian women disappeared, but remained significant for Caucasian–Asian differences in the effect of T1DM on LGA neonates (Caucasian: aRR 4.83, 95% CI (4.40 to 5.30); Asian: aRR 1.47, 95% CI (0.89 to 2.41)) (online supplemental table S3).

DISCUSSION

In this large, population-based cohort study in the Canadian province of Ontario, we find that rates of T1DM and

LGA in Caucasians were two times of that in Asians, and the relative risk of T1DM on LGA was significantly higher in Caucasians than that in Asians. The contribution of T1DM to LGA ranked fourth in Caucasians while ranked seventh in Asians.

To our knowledge, this is the first study examining the Caucasian–Asian differences in the association between T1DM and LGA. According to the 2016 Canada Census data, Asians were the largest and fastest-growing visible minority group, accounting for 17.7% Canada's total population and 23.4% in Ontario.²⁶ Using a contemporary and population-based registry with a robust modeling strategy and adjusting rich important confounders resulted in a stable estimated association between T1DM and LGA in each race group. Our study

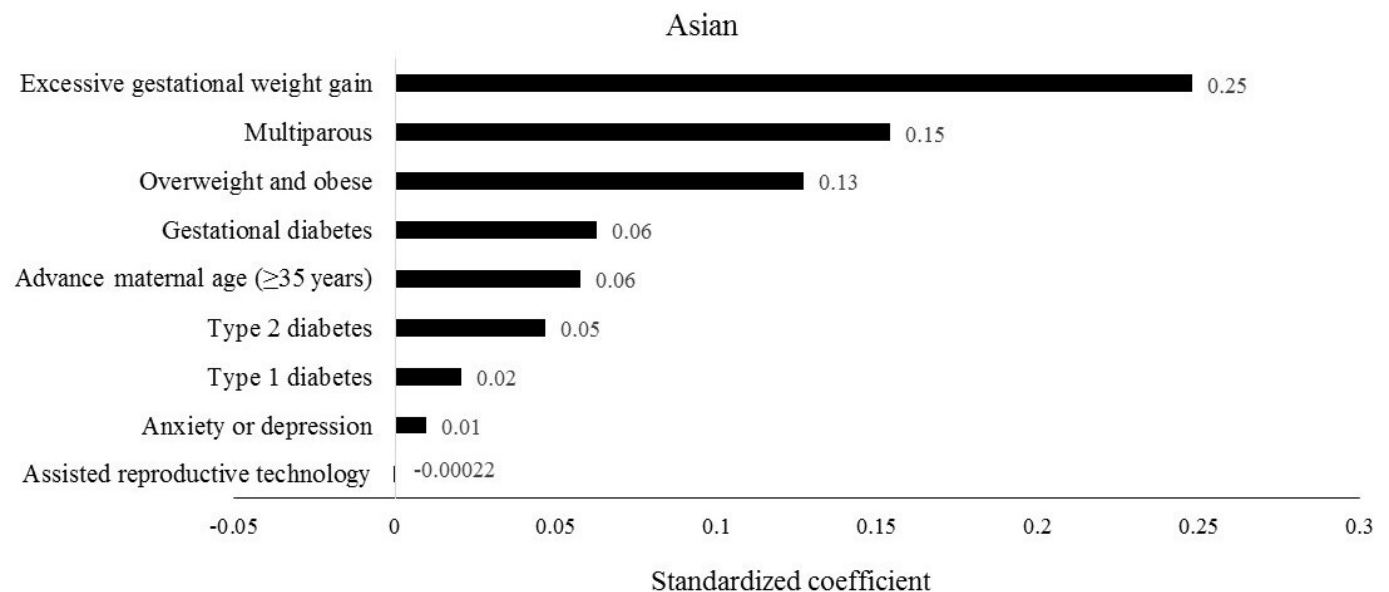


Figure 3 Contribution (standard coefficient) of each risk factor to large-for-gestational-age neonates among Asian women.

has a large sample size of Asian women, enabling a robust comparison of the role of T1DM on LGA between Caucasians and Asians in the context of a universal access healthcare system. Similar comparisons may be difficult to obtain in the USA and Europe due to the relatively small proportion of Asian population and multiple health insurance providers.^{27 28} Our finding of a higher T1DM rate in Caucasians was similar to a national study in the USA, showing that Asians have a much lower prevalence of T1DM compared with Caucasians (0.6% for non-Hispanic white and 0.2% for non-Hispanic Asian).²⁹ Moreover, our findings further supported the Caucasian–Asian differences in the LGA rate, which was well documented in previous studies.^{30 31} In addition to assessing the modification effect of race on the association between T1DM and LGA, we quantified the relative contribution of different risk factors on LGA between Caucasians and Asians. It is interesting to find that T1DM ranked fourth-strongest contributor to LGA among Caucasians, following excessive gestational weight gain, multiparous, and high BMI. On the other hand, T1DM ranked the seventh contributor of LGA in Asian women, following excessive gestational weight gain, multiparous, high BMI, gestational diabetes, advanced maternal age, and T2DM. Our findings supported previous studies that high BMI or obesity and excessive gestational weight gain were the top two modifiable risk factors of LGA for both Caucasian and Asian women.^{31–35} We provided further evidence that T1DM had a more significant contribution to LGA neonates in Caucasians than Asians. Our finding also demonstrated that gestational diabetes was contributed to LGA neonates, which was consistent with the report that gestational diabetes was associated with LGA trajectory at week 20 and became significant at gestational week 28.³⁶

Our findings of racial variations in T1DM and significant differences in the effect of T1DM on LGA by race have raised the need for better understanding the hypothesis of unique mechanisms of the development of T1DM across different races.^{37 38} Resulting from the beta-cell destruction and absolute insulin deficiency, susceptibility to T1DM involves a strong genetic component,³⁹ especially genes encoded HLA had the highest genetic risk for disease. Heterogeneity of T1DM has been documented in the population, where the genetic, immunologic, metabolic, and clinical presentations and outcomes may vary between Caucasian and Asian considerably.⁴⁰ The racial variation of immune-genetic characteristics presented by Nobel⁴¹ that the frequency of high-risk immune-genetic alleles, haplotypes or genotypes, and their susceptibility or protective effects for T1DM risk differed among populations including Caucasians and Asians. The protective allele for T1DM has been so far reported with a higher frequency among Asian descents (~3.5%) compared with Europeans (0.6%).⁴² Therefore, the beta cell destruction may be less potent in Asians. The variable association of the HLA-associated phenotypes to clinical onset and severity-related characteristics of autoimmune diabetes

by race/ethnicity may partially explain the discrepancies of the effect of T1DM on LGA between Caucasians and Asians.⁴³

Given the complexities of medical and social contexts associated with race and racial bias in healthcare, understanding the role of race in the effect of T1DM on LGA is valuable to inform clinical practices on prenatal management to reduce T1DM-associated morbidity in the offspring. Some studies have shown that race is more of a social construct than a biological construct. The effect of race on health outcomes tends to diminish significantly when socioeconomic status is controlled for and, in some instances, the race effect disappears.⁴⁴ However, our study of Caucasian–Asian variations in the effect of T1DM on LGA seems driven by a genetic model that the Caucasian–Asian difference is determined predominantly by biological factors. Although this study uses an extensive retrospective population-based registry with adjustment for multiple biological, care practice, and socioeconomic variables, the lack of environmental and genetic contribution measurements and their interactions will limit our explanation of the moderator effect of race on T1DM and LGA.⁴⁵ In addition, race was reported by the mother alone in our study, although self-reported maternal race and infant genetic ancestry are closely related.⁴⁶ In general, self-reported race is most reliable and should be the preferred method. However, with the increase in the number of people that belong to multiple racial categories, it is increasingly difficult to classify individuals into one race category, which further complicates the interpretation of race effects in research studies.^{47 48} We were unable to differentiate subgroups of South Asian and East Asian women in BORN birth registry. Previous studies have reported that the relationships between obesity and excessive gestational weight gain differ between East and South Asian groups.^{49 50}

Other limitations were also indicated in the current study. First, we did not have glycemic control and maternal lipid levels data available in our study.² Second, although consistent with literature reports, events of T1DM, T2DM, gestational diabetes may have been misclassified by coding errors or missed if the hyperglycemic code was not selected as the primary diagnosis. Third, to examine the robustness of our main results, we use two birthweight references to identify LGA. However, when using racial-specific birthweight curves to LGA, the difference of LGA disappeared, but the effect of T1DM on LGA between Caucasian and Asian were still significantly different. Although we used largest Canadian birth registry for this study, due to the low prevalence of T1DM in Asian women, the effect of T1DM on LGA disappeared when using racial-specific birthweight curve to identify LGA. Further data with larger sample size are needed to validate our findings. Finally, selection bias may have resulted from exclusion of women who did not complete prenatal screening, and we do not know the direction and magnitude of such potential bias. Women who underwent prenatal screening were more likely to

live in an urban area, receive care from an obstetrician, have a higher income, and have immigrant or refugee status.⁵¹ The results generation will be caution.

In summary, our study showed that T1DM had a much greater impact on LGA in Caucasians than Asians under universal healthcare system. Among common risk factors, T1DM appears to be a more important risk factor of LGA neonates in Caucasians than Asians. Further research is warranted to better understand the etiology of Caucasian–Asian difference in T1DM on LGA, which will not only promote future prediction and prevention of LGA but also inform the clinical management practices of patients with T1DM.

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