


Sex dimorphism in the associations of gestational diabetes with cord blood adiponectin and retinol-binding protein 4

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ABSTRACT

Introduction Gestational diabetes (GD) is associated with impaired insulin sensitivity in newborns. Adiponectin and retinol-binding protein 4 (RBP-4) are involved in regulating insulin sensitivity. Females are more likely to develop diabetes at young ages than males. We tested the hypothesis that GD may affect RBP-4 and adiponectin levels in early life, and there may be sex-dimorphic associations.

Research design and methods In a nested case-control study of 153 matched pairs of neonates of mothers with GD and euglycemic pregnancies in the Shanghai Birth Cohort, we evaluated cord plasma leptin, high molecular weight (HMW) and total adiponectin and RBP-4 concentrations.

Results Comparing GD versus euglycemic pregnancies adjusted for maternal and neonatal characteristics in female newborns, cord plasma total adiponectin (mean±SD: 30.8±14.3 vs 37.1±16.1 µg/mL, p=0.048) and HMW adiponectin (14.6±7.7 vs 19.3±8.3 µg/mL, p=0.004) concentrations were lower, while RBP-4 concentrations were higher (21.7±5.4 vs 20.0±4.8 µg/mL, p=0.007). In contrast, there were no differences in male newborns (all p>0.2). RBP-4 concentrations were higher in female versus male newborns (21.7±5.4 vs 18.8±4.5 µg/mL, p<0.001) in GD pregnancies only. HMW adiponectin concentrations were significantly higher in female versus male newborns in euglycemic pregnancies only (19.3±8.3 vs 16.1±7.4 µg/mL, p=0.014).

Conclusions GD was associated with lower cord plasma HMW adiponectin and higher RBP-4 concentrations in female newborns only. The study is the first to reveal a sex-dimorphic early life impact of GD on metabolic health biomarkers in the offspring. GD may alter the normal presence (HMW adiponectin) or absence (RBP-4) of sex dimorphism in some insulin sensitivity regulation-relevant adipokines in early life.

INTRODUCTION

Gestational diabetes (GD) is a common metabolic disorder of pregnancy characterized by insulin resistance and altered glucose-lipid metabolism.¹ The offspring of GD mothers

Significance of this study

What is already known about this subject?

- ▶ Adiponectin and retinol-binding protein 4 (RBP-4) are involved in regulating insulin sensitivity.
- ▶ Gestational diabetes is associated with impaired insulin sensitivity in newborns. Gestational diabetes may affect adiponectin and RBP-4 levels in early life, and it is unknown whether there is any sex-dimorphic association.

What are the new findings?

- ▶ Gestational diabetes is associated with lower cord plasma high molecular weight (HMW) adiponectin and higher RBP-4 concentrations in female newborns but not in male newborns, suggesting a sex-dimorphic early life impact on the offspring.
- ▶ Gestational diabetes may alter the normal presence (HMW adiponectin) or absence (RBP-4) of sex dimorphism in some insulin sensitivity regulation-relevant adipokines in early life.

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

- ▶ There may be a sex-dimorphic impact of gestational diabetes on metabolic health in the offspring in early life. Further studies are required to understand the long-term metabolic health implications that may inform the development of sex-specific early life interventions to decrease the vulnerability to diabetes.

are at elevated risk of obesity and impaired glucose tolerance during adolescence, and increased risk of diabetes in later life.^{2,3} How this increased susceptibility to metabolic dysfunctional disorders is developed in early life remains unclear. Impaired insulin sensitivity has been observed in the newborns of mothers with GD,⁴ and in large for gestational age (often a suspected consequence of varying degrees of hyperglycemia in pregnancy)

newborns,⁵ Plausibly, altered levels of insulin sensitivity regulating adipokines may be involved.

Leptin and adiponectin are important adipokines in regulating insulin sensitivity.⁶ Adiponectin exists in low, medium and high molecular weight (HMW) forms, and HMW adiponectin is recognized as the most bioactive form of adiponectin as related to its insulin-sensitizing property.⁶ Studies have reported elevated cord blood leptin and decreased adiponectin levels in GD,^{7–9} but no significant differences have also been observed in some studies.¹⁰ Retinol-binding protein 4 (RBP-4) is an adipokine implicated in insulin resistance.¹¹ Circulating RBP-4 concentration was positively correlated with insulin resistance in subjects with obesity and type 2 diabetes.¹² There have been inconsistent data concerning whether there are significant changes in maternal circulating RBP-4 levels in GD.^{13–17} We are aware of only one study on cord blood RBP-4 levels in GD pregnancies.⁹

Studies have demonstrated that females are more insulin resistant than males in utero,^{18,19} and more likely to develop diabetes at young ages.^{20,21} It is unclear whether the early life origins of such elevated vulnerability in females may be related to any alterations in insulin sensitivity regulating adipokines such as leptin, adiponectin and RBP-4. Sex dimorphisms in cord blood leptin and adiponectin concentrations have been reported, possibly attributable to the effects of body fat.^{7,22} It is unknown whether GD may affect any sex dimorphism in fetal (cord) blood levels of leptin, adiponectin and RBP-4.

In view of the above-described knowledge gaps, the present study sought to determine whether there are alterations in cord blood leptin, adiponectin and RBP-4 levels in GD, and assess whether there is sex dimorphism in the associations of GD with cord blood RBP-4, leptin and adiponectin levels in a large birth cohort.

RESEARCH DESIGN AND METHODS

Study design, subjects and specimens

This study was based on the recently described Shanghai Birth Cohort (SBC).²³ The SBC is a large, carefully phenotyped pregnancy/birth cohort with linked biospecimen bank for studies on perinatal determinants of infant growth, development and health. Women at preconception or early pregnancy care clinics were recruited from six urban university-affiliated tertiary obstetric care hospitals in Shanghai between 2013 and 2016 and including a total of 4127 pregnancies. The women were followed up at the first, second and third trimesters of pregnancy and delivery. Data and specimens were collected at each study visit. All collected blood samples were kept on ice, stored temporarily in a 4°C refrigerator and centrifuged within 2 hours after the specimen collection. The separated serum and EDTA plasma samples were stored in multiple aliquots at –80°C until assays.

Maternal pre-pregnancy body mass index (BMI, in kg/m²) was calculated as pre-pregnancy weight (self-reported)

divided by squared height (measured in the first prenatal care visit). GD was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups criteria²⁴—if any one of the blood glucose values was at or above the following thresholds in the 75 g oral glucose tolerance test at 24–28 weeks of gestation: fasting 5.1 mmol/L, 1-hour 10.0 mmol/L and 2-hour 8.5 mmol/L.

As part of the SBC project, we conducted a nested case-control study on cord blood biomarkers in GD.²⁵ The present study reported the original data on the impacts of GD and fetal sex on cord blood leptin, adiponectin and RBP-4 levels (a priori planned study objective). Cases were the newborns of GD mothers, and controls were the newborns of euglycemic mothers. We did not have the data on whether GD mothers were hyperglycemic at the time of delivery (cord blood specimen collection). All cases and controls must meet the following eligibility criteria: (1) Han ethnicity (the majority ethnic group, >98%); (2) maternal age 20–45 years; (3) natural conception; (4) singleton pregnancy; (5) the mother was free of severe pre-pregnancy illnesses (eg, type 1 or type 2 diabetes, and chronic hypertension) and life-threatening pregnancy complications (eg, pre-eclampsia/eclampsia); (6) the infant was free of birth defects; (7) 5 min Apgar score ≥ 7 ; and (8) cord blood and placenta specimens available for future assays. All eligible newborns of GD mothers (n=153) were included. Controls were randomly sampled among all eligible subjects and matched to cases (1:1) by infant sex (the same) and gestational age (within 1 week). Therefore, a total of 306 subjects (153 GD; 153 controls) constituted the study sample.

Biochemical assays

Cord plasma RBP-4 was measured by an ELISA kit (R&D Systems, Minnesota, USA), and the absorbance was determined using a microplate spectrophotometer (Beckman CX7, USA). Plasma HMW and total adiponectin were measured by an ELISA kit from ALPCO (Salem, NH, USA), and plasma leptin by an ELISA kit from Invitrogen (Carlsbad, CA, USA), respectively. The detection limits were 0.22 ng/mL for RBP-4, 0.034 ng/mL for HMW and total adiponectin, and 3.5 pg/mL for leptin, respectively. Intra-assay and interassay coefficients of variation were in the ranges of 5.0%–8.6% for RBP-4, and 6.9%–10.4% for leptin, HMW and total adiponectin, respectively. In all biomarker assays, the laboratory technicians were blinded to the clinical status (GD or not) of study subjects.

Statistical analysis

The primary outcomes were cord plasma leptin, HMW adiponectin and RBP-4 concentrations. Paired t-test was used to compare continuous variables in GD and control groups, and McNemar's χ^2 test was used for comparisons of dichotomous variables. Pearson partial correlation analysis was used to evaluate the correlations between biomarkers adjusting for gestational age at delivery/blood sampling. Log-transformed biomarker data were used in t-tests, correlation and regression analyses.

Generalized linear models were applied to assess the differences in cord blood RBP-4, leptin and adiponectin concentrations (by GD status or fetal sex) adjusted for maternal and neonatal characteristics, and in tests for interactions (as multiplicative terms). Maternal and neonatal characteristic variables included maternal age, ethnicity (all Chinese Han), parity, education (university: yes/no), pre-pregnancy BMI (kg/m^2), gestational weight gain (z score), smoking or alcohol use in pregnancy (yes/no), GD, gestational hypertension, family history of diabetes, family history of hypertension, mode of delivery (cesarean section/vaginal), infant sex, gestational age (weeks) and birth weight (z score). Parsimonious final regression models were fitted in evaluating the adjusted effects excluding covariables that were not associated with the outcomes ($p>0.2$) and did not affect the comparisons. Data management and analyses were performed in SAS V.9.4 (SAS Institute). Two-tailed p value <0.017 was considered statistically significant in testing the hypothesis concerning the differences in the three primary outcomes comparing GD versus control groups (Bonferroni correction for three comparisons). A relatively lenient p value <0.10 was considered significant in regression tests of interactions to allow better chance of identifying potentially important interactions.

RESULTS

Maternal and neonatal characteristics

Characteristics of the study subjects were described recently.²⁵ Briefly, women with GD had higher pre-pregnancy BMI than euglycemic women (mean \pm SD: 23.6 \pm 4.3 vs 21.6 \pm 2.9 kg/m^2 , $p<0.001$), and were more likely to have gestational hypertension (5.2% vs 0.6%, $p=0.036$),

and tended to be more likely to have a family history of diabetes (16.5% vs 9.5%, $p=0.072$). There were no significant differences in other maternal characteristics including maternal age (30.4 \pm 3.7 vs 29.9 \pm 3.4 years), education (university 62.8% vs 60.5%), parity (primiparous 81.1% vs 81.7%), alcohol use (7.1% vs 11.3%) and smoking during pregnancy (only three smokers) (all $p>0.1$). Newborns of GD mothers were more likely to be delivered by cesarean section than newborns of euglycemic mothers (54.3% vs 33.1%, $p<0.001$). Despite the matching for infant sex and gestational age at delivery (within 1 week), mean gestational age at delivery was slightly shorter comparing GD versus euglycemic pregnancies (39.1 \pm 1.2 vs 39.3 \pm 1.2 weeks, $p<0.001$), while average birth weight tended to be higher (3435.9 \pm 488.7 vs 3354.6 \pm 435.6 g, $p=0.093$).

Cord plasma RBP-4, leptin and adiponectin in GD and euglycemic pregnancies

Adjusting for maternal and neonatal characteristics including pre-pregnancy BMI, family history of hypertension, gestational hypertension, family history of diabetes, cesarean section, and gestational age at delivery (other covariates did not affect the comparisons), cord plasma HMW adiponectin concentrations and HMW/total adiponectin ratios were lower in GD versus euglycemic pregnancies in the total study sample (table 1). However, there were no significant differences in cord plasma RBP-4, total adiponectin and leptin concentrations between the two groups.

Sex-specific associations of GD with RBP-4, leptin and adiponectin

Adjusted for maternal and neonatal characteristics, there were no significant differences in all observed cord blood

Table 1 Cord plasma RBP-4, leptin, HMW and total adiponectin concentrations in the newborns of GD versus control (euglycemic) mothers

	GD (n=153)	Control (n=153)	Crude P value*	Adjusted P value*
RBP-4 ($\mu\text{g}/\text{mL}$)	20.1 \pm 5.1 19.5 (16.8, 23.2)	19.7 \pm 5.0 19.0 (15.9, 22.7)	0.562	0.204
Leptin (ng/mL)	7.3 \pm 7.3 4.6 (2.8, 9.4)	8.1 \pm 7.1 5.9 (3.6, 9.9)	0.074	0.341
Adiponectin, HMW ($\mu\text{g}/\text{mL}$)	15.0 \pm 7.5 14.3 (10.1, 18.8)	17.6 \pm 8.0 16.3 (12.1, 21.6)	0.002	0.006
Adiponectin, total ($\mu\text{g}/\text{mL}$)	33.2 \pm 15.0 31.7 (23.5, 42.6)	36.3 \pm 15.8 33.1 (24.7, 46.1)	0.073	0.071
HMW/total ratio	0.46 \pm 0.15 0.44 (0.36, 0.51)	0.50 \pm 0.14 0.49 (0.41, 0.56)	0.003	0.032

Data presented are mean \pm SD and median (IQR).

P values in bold: $p<0.017$ (significant after accounting for multiple tests of the differences in the three primary outcomes (leptin, HMW adiponectin and RBP-4) between GD and control groups).

*Crude p values were from paired t-tests in log-transformed data. Adjusted p values were from generalized linear models in the comparisons of log-transformed biomarker data between the two groups adjusted for maternal (pre-pregnancy BMI, family history of diabetes, family history of hypertension, gestational hypertension) and neonatal (cesarean section) characteristics; other factors were excluded since they were similar and did not affect the comparisons ($p>0.2$).

BMI, body mass index; GD, gestational diabetes; HMW, high molecular weight; RBP-4, retinol-binding protein 4.

Table 2 Cord plasma RBP-4, leptin and adiponectin concentrations in the newborns of GD versus control (euglycemic) mothers stratified by infant sex

	Male newborns		Crude P value*	Adjusted P value*	Female newborns		Crude P value*	Adjusted P value*
	GD	Control			GD	Control		
RBP-4 (µg/mL)	18.8±4.5	19.4±5.1	0.383	0.594	21.7±5.4	20.0±4.8	0.078	0.007
Leptin (ng/mL)	5.5±5.0	7.0±6.7	0.231	0.268	9.6±8.9	9.3±7.4	0.416	0.690
Adiponectin								
HMW (µg/mL)	15.3±7.4	16.1±7.4	0.312	0.354	14.6±7.7	19.3±8.3	0.002	0.004
Total (µg/mL)	35.1±15.2	35.6±15.6	0.754	0.485	30.8±14.3	37.1±16.1	0.025	0.048
HMW/total	0.45±0.16	0.47±0.14	0.279	0.682	0.47±0.13	0.53±0.13	0.001	0.003

Data presented are mean±SD. There were 140 male newborns (of 70 GD and 70 euglycemic mothers) and 166 female newborns (of 83 GD and 83 euglycemic mothers) in the analyses.

P values in bold: $p < 0.017$ (significant after accounting for multiple tests of the differences in the three primary outcomes (leptin, HMW adiponectin and RBP-4) between GD and control groups).

*Crude p values were from paired t-tests in log-transformed data. Adjusted p values were from generalized linear models in the comparisons of log-transformed biomarker data between the two groups adjusted for maternal (pre-pregnancy BMI, family history of diabetes, family history of hypertension, gestational hypertension) and neonatal (cesarean section) characteristics; other factors were excluded since they were similar and did not affect the comparisons ($p > 0.2$).

BMI, body mass index; GD, gestational diabetes; HMW, high molecular weight; RBP-4, retinol-binding protein 4.

biomarkers between GD and non-GD groups in male newborns (table 2). In contrast, for female newborns, GD was associated with higher cord plasma RBP-4 concentrations (adjusted $p = 0.007$), but lower HMW adiponectin (adjusted $p = 0.004$) and total adiponectin (adjusted $p = 0.048$, not significant if accounting for multiple tests) concentrations, and lower HMW/total adiponectin ratios. The p values in tests for interactions of GD with infant sex were 0.094 for RBP-4, 0.035 for HMW adiponectin, 0.114 for total adiponectin, and 0.198 for HMW/total adiponectin ratio, respectively. The adjusted differences (in log scale) are presented in table 3, and the findings were similar as in table 2.

Sex differences in cord blood RBP-4, leptin and adiponectin

In GD pregnancies, female newborns had significantly higher cord plasma RBP-4 concentrations than male

newborns (21.7±5.4 vs 18.8±4.5 ng/mL, $p < 0.001$), while there was no sex difference in euglycemic pregnancies ($p = 0.43$). In euglycemic pregnancies, there were higher HMW adiponectin concentrations ($p = 0.014$) and HMW/total adiponectin ratios ($p = 0.006$) in female versus male newborns, while these differences disappeared in GD pregnancies ($p = 0.59$ for HMW adiponectin; $p = 0.47$ for HMW/total adiponectin ratio). Cord plasma leptin levels were higher in female versus male newborns regardless of GD status ($p = 0.001$ in GD; $p = 0.045$ in controls).

Partial correlations

Adjusting for gestational age at blood sampling, cord plasma RBP-4 was weakly and positively correlated to leptin and birth weight z score, but not correlated to adiponectin (table 4). As expected, HMW and total adiponectin were strongly correlated. Leptin was

Table 3 The adjusted differences in cord blood biomarkers between GD and controls in male and female newborns

	Males			Females		
	β	95% CI	Adjusted P value	β	95% CI	Adjusted P value
RBP-4 (µg/mL)	-0.02	(-0.11 to 0.06)	0.594	0.13	(0.04 to 0.22)	0.007
Leptin (ng/mL)	-0.16	(-0.45 to 0.13)	0.268	-0.06	(-0.34 to 0.22)	0.690
Adiponectin						
HMW (µg/mL)	-0.07	(-0.23 to 0.08)	0.354	-0.33	(-0.56 to -0.11)	0.004
Total (µg/mL)	-0.05	(-0.20 to 0.10)	0.485	-0.19	(-0.37 to -0.002)	0.048
HMW/total ratio	-0.02	(-0.12 to 0.08)	0.682	-0.15	(-0.24 to -0.05)	0.003

Data (β) presented are the regression coefficients for GD (yes vs no) from generalized linear models of log-transformed biomarker data with the adjustments for maternal (pre-pregnancy BMI, family history of diabetes, family history of hypertension, gestational hypertension) and neonatal (cesarean section) characteristics; other factors were excluded since they were similar and did not affect the comparisons between the two groups.

P values in bold: $p < 0.017$ (significant after accounting for multiple tests of the differences in the three primary outcomes (leptin, HMW adiponectin, RBP-4) between GD and controls).

BMI, body mass index; GD, gestational diabetes; HMW, high molecular weight; RBP-4, retinol-binding protein 4.

Table 4 Partial correlation coefficients (r) between cord blood RBP-4, leptin, HMW and total adiponectin and birth weight z score

	RBP-4	Leptin	HMW adiponectin	Total adiponectin
Leptin	0.13*			
Adiponectin, HMW	0.07	0.18**		
Adiponectin, total	0.05	0.09	0.85***	
Birth weight, z score	0.15**	0.37***	0.12*	0.15*

Data presented are Pearson partial correlation adjusting for gestational age at delivery/cord blood sampling.

*P<0.05; **p<0.01; ***p<0.001.

HMW, high molecular weight; RBP-4, retinol-binding protein 4.

positively correlated to HMW adiponectin. Sex-stratified analyses showed that RBP-4 was positively correlated with leptin in female newborns but not in male newborns (table 5).

DISCUSSION

Main findings

The study is the first to reveal sex-dimorphic associations of GD with cord blood RBP-4 and adiponectin concentrations. GD was associated with elevated cord blood RBP-4 and decreased HMW adiponectin concentrations in female newborns but not in male newborns. The study is the first to demonstrate that GD may affect the normal presence (HMW adiponectin) or absence (RBP-4) of sex dimorphism in some insulin sensitivity regulation-relevant adipokines in early life.

Data interpretation and comparisons to findings in previous studies

Adipokines play a critical role in the regulation of glucose homeostasis and insulin sensitivity,^{12 26} and may provide an important link between obesity-related disorders and insulin resistance.^{27 28} RBP-4 is involved in regulating glucose metabolism and insulin sensitivity.^{12 29} Some studies have reported higher maternal serum RBP-4 levels in GD women.^{9 13 14} Two studies^{9 13} reported no significant differences in cord serum RBP-4 concentrations between GD and control groups, but they did not report sex-specific comparisons. In contrast, our

data showed that GD was associated with elevated cord plasma RBP-4 concentrations in female newborns only, suggesting that GD may have a sex-dimorphic impact on metabolic health during fetal life.

Two studies reported that total or HMW adiponectin concentrations in cord serum did not differ between GD and controls,^{30 31} whereas two other studies reported lower cord serum or plasma adiponectin concentrations in GD.^{8 9} In contrast, we observed that GD was associated with decreased cord plasma adiponectin (more substantially for HMW adiponectin) concentrations in female newborns, but not in male newborns. Previous studies did not provide sex-specific data. Our data from a nested case-control study in a much larger cohort suggest a sex-dimorphic impact of GD on cord blood adiponectin concentration.

Some studies in adolescents or adults reported sex differences in circulating RBP-4 levels,^{29 32} while others did not.³³ Serum RBP-4 concentrations were observed to be lower in female than male subjects in children and adults.^{29 34 35} There is a lack of data on sex difference in cord blood RBP-4. We observed no sex difference in cord plasma RBP-4 concentrations in euglycemic pregnancies, but higher concentrations in female newborns in GD pregnancies. The mechanisms are unclear. We speculate that this may be due to the altered metabolic milieu in GD with pronounced insulin resistance.³⁶

Higher total adiponectin circulating concentrations in females versus males have been reported in children, adolescents and adults.³⁷⁻³⁹ This sex dimorphism appears to be primarily related to the HMW adiponectin complexes.^{39 40} Our data in euglycemic pregnancies suggest that this sex dimorphism in HMW adiponectin may be established in utero in normal (euglycemic) pregnancies (higher cord plasma HMW adiponectin concentrations in female vs male neonates). HMW adiponectin levels may vary by fetal sex even at the early stage of human development. We speculated that this sex dimorphism could be related to the effects of androgens. Testosterone may selectively reduce HMW adiponectin secretion from adipocytes,^{41 42} and higher testosterone concentrations in male versus female fetuses⁴³ may contribute to the lower HMW concentrations in male newborns. Androgens may indirectly regulate adiponectin distribution through a decrease in adipocyte number and size in male fetuses.^{44 45}

Table 5 Correlations of cord plasma RBP-4 with leptin, HMW and total adiponectin in male and female newborns

	Males		Females	
	r	P value	r	P value
Leptin	0.012	0.884	0.2147	0.013
Adiponectin				
HMW	0.145	0.067	-0.010	0.912
Total	0.123	0.121	-0.005	0.952
HMW/total ratio	0.078	0.377	-0.059	0.947

Data presented are Pearson partial correlations (r) adjusting for gestational age at delivery/cord blood sampling.

P values in bold: p<0.05.

HMW, high molecular weight; RBP-4, retinol-binding protein 4.

Importantly, our study is the first to reveal that such physiological sex difference in cord blood HMW adiponectin levels may be lost in GD pregnancies.

Strengths and limitations

The main strengths include the large birth cohort, timely collection and processing of blood specimens and high-quality biochemical assays (low intra-assay and interassay coefficients of variation), and sex-specific data. The main limitation is the observational nature of the study. We could not rule out the possibility of reverse causality. The study was limited to Chinese Han ethnicity subjects. While such study design confers the advantage of enhanced power to uncover biological relationships in the absence of the potential confounding effects of race/ethnicity, it also calls for more studies in other race/ethnic groups to understand the generalizability of the study findings.

CONCLUSIONS

GD may affect cord blood RBP-4 and adiponectin levels in female newborns but not in male newborns. GD may alter the normal presence (HMW adiponectin) or absence (RBP-4) of sex dimorphism in some insulin sensitivity regulation-relevant adipokines in early life. Further studies are required to understand the long-term metabolic health implications, and physicians may be informed for better counseling of patients, and this knowledge will inform the development of early life sex-specific interventions to decrease the vulnerability to diabetes in future generations.

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the literature review and data analysis and drafted the manuscript. All authors contributed in revising the article critically for important intellectual content, and approved the final version for publication.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Access to the deidentified participant research data must be approved by the research ethics board on a case-by-case basis; please contact the corresponding author (zcluo@lunenfeld.ca; huaxiaolin_sh@163.com) for assistance in data access request.

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