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Effect of gestational diabetes and hypertensive disorders of pregnancy on postpartum cardiometabolic risk

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Abstract

Aims: The cumulative effect of gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP) on postpartum cardio-metabolic diseases is equivocal. We aimed to assess the associations of GDM and HDP's individual and synergic contribution to risks of postpartum cardio-metabolic diseases (metabolic syndrome (MetS), abnormal glucose metabolism and hypertension (HTN)).
Methods: Of participants from a Singapore birth cohort, 276 mothers attending the 5-year postpartum visit were included in this study. During this visit, we collected mothers' history of GDM and HDP in all live births in a chronicle sequence and assessed the cardio-metabolic risks based on blood pressure, anthropometry and a panel of serum biomarkers. We diagnosed MetS, abnormal glucose metabolism and HTN according to Adult Treatment Panel III 2000 and World Health Organization guidelines.
Results: Of 276 mothers, 157 (56.9%) had histories of GDM while 23 (8.3%) had histories of HDP. After full adjustment, we found associations of GDM episodes with postpartum abnormal glucose metabolism (single episode: relative risk (RR) 2.9 (95% CI: 1.7, 4.8); recurrent episodes ($\geq$2): RR = 3.8 (2.1–6.8)). Also, we found association between histories of HDP and HTN (RR = 3.6 (1.5, 8.6)). Having either (RR 2.6 (1.7–3.9)) or both gestational complications (RR 2.7 (1.6–4.9)) was associated with similar risk of postpartum cardio-metabolic disease.
Conclusions: Mothers with GDM or HDP had a threefold increased risk of postpartum abnormal glucose metabolism or HTN, respectively. Having both GDM and HDP during past pregnancies was not associated with additional risk of postpartum cardio-metabolic diseases beyond that associated with either complication alone.

Key Words
- ▶ gestational diabetes mellitus
- ▶ hypertensive disorders of pregnancy
- ▶ cardio-metabolic disease
- ▶ metabolic syndrome
- ▶ hypertension
- ▶ abnormal glucose metabolism

Introduction

Gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP) are two of the most commonly seen pregnancy complications that adversely affect both short-term and long-term maternal and fetal outcomes (1, 2, 3). The diagnosis of GDM identifies women with insulin resistance (targeted cell resistance to the

activity of insulin) and/or β-cell dysfunction (insufficient secretion of insulin by the pancreatic β-cells to compensate for peripheral insulin resistance) during pregnancy (4, 5). After pregnancy, GDM mothers are susceptible to progressive worsening in chronic β-cell defects, which is believed to mediate the development of recurrent GDM in subsequent pregnancy and postpartum type 2 diabetes (T2D) (5, 6, 7). Consistent epidemiological evidence has shown that among mothers with prior history of GDM, 30–84% had GDM recurrence in subsequent pregnancies (8), 20–40% developed metabolic syndrome (MetS) within 2–20 years (9, 10), 17–63% developed T2D within 5–16 years (11, 12), and 10% developed renal disease within 11 years after delivery (13).

Interestingly, HDP including gestational hypertension, preeclampsia (PE) and eclampsia is more frequent among GDM mothers (14, 15). Studies suggested that gestational hypertension and PE were more likely to be an accompanying co-morbidity in pregnancies complicated with GDM, and could recur in subsequent pregnancies in mothers prior to GDM (16, 17). Conditions associated with increased insulin resistance may predispose patients to essential hypertension, pregnancy-induced hypertension, hyperinsulinemia, hyperlipidemia and higher levels of plasminogen activator inhibitor-1, leptin and tumor necrosis factors-alpha (16, 18).

However, even though these two conditions may co-exist in the same or different pregnancies of the same mothers, evidence in the literature is inconsistent regarding whether or not co-existent GDM and HDP has a synergic effect to the risk of postpartum cardio-metabolic disease (17). In a cohort of 276 mothers who had comprehensive data on history of GDM and HDP and full assessments on postpartum cardio-metabolic diseases, we aimed to investigate the following questions: The impact of recurrent GDMs, HDP or co-existence of both pregnancy complications, on the risk of postpartum cardio-metabolic diseases, including metabolic syndrome (MetS), abnormal glucose metabolism and hypertension (HTN).

Methods

Study population and design

This was a prospective study nested in an ongoing birth cohort in Singapore (Growing Up in Singapore Towards Healthy Outcomes, GUSTO). We previously reported the GUSTO study design and recruitment criteria in detail (19). Of mothers who were recruited to the GUSTO during early trimester (5–8 weeks) of their baseline pregnancy, we intended to include 400 in this study; of whom 200 were diagnosed with GDM at baseline pregnancy, the remaining 200 were controls without GDM at baseline pregnancy, matched to GDM mothers for age, ethnicity and body mass index (BMI). This matched cohort of mothers with and without GDM was designed to investigate antenatal risk factors, and GDM particularly, associated with the development of postpartum cardio-metabolic diseases.

Inclusion criteria are (1) Mothers who attended both baseline and 5-year follow-up visits; (2) Mothers without chronic hypertension and/or diabetes at baseline recruitment and (3) Mothers who were not pregnant at the 5-year follow-up visit. Among 400 mothers originally selected from 1136 mothers in the GUSTO, 354 met the inclusion criteria. After excluding 47 mothers who declined participation and 31 who withdrew after consenting, a total number of 276 mothers (response rate 78.0%) were included in this report (Fig. 1).

We diagnosed GDM as fasting glucose ≥7.0 mmol/L and/or 2-h glucose ≥7.8 mmol/L at 26- to 28-week gestation of baseline pregnancy, according to 1999 WHO guideline via a 75 g oral glucose tolerance test (20).

We conducted the study according to the tenets of the Declaration of Helsinki and obtained approval by the SingHealth Centralized Institutional Review Board and the National Health Group's Domain Specific Review Board. We obtained written informed consents from all participants at the 5-year follow-up visit .

Exposure: histories of GDM and HDP

Trained staff administered a detailed pregnancy and birth outcomes questionnaire to all mothers attending the 5-year follow-up visit. We recorded all past pregnancies including miscarriage, abortion, stillbirths and live births in a chronicle sequence. For all pregnancies, we collected time (in year format) and outcomes of each pregnancy. For live births, we further collected pregnancy complications of GDM and HDP (a cluster of gestational hypertension, preeclampsia and eclampsia) based on mothers' self-reporting.

We categorized GDM episodes into three groups: (1) Never; (2) One; (3) ≥2 (recurrent). However, due to low number of HDP episodes, we dichotomized HDP into two groups only: (1) Never; (2) One or more.
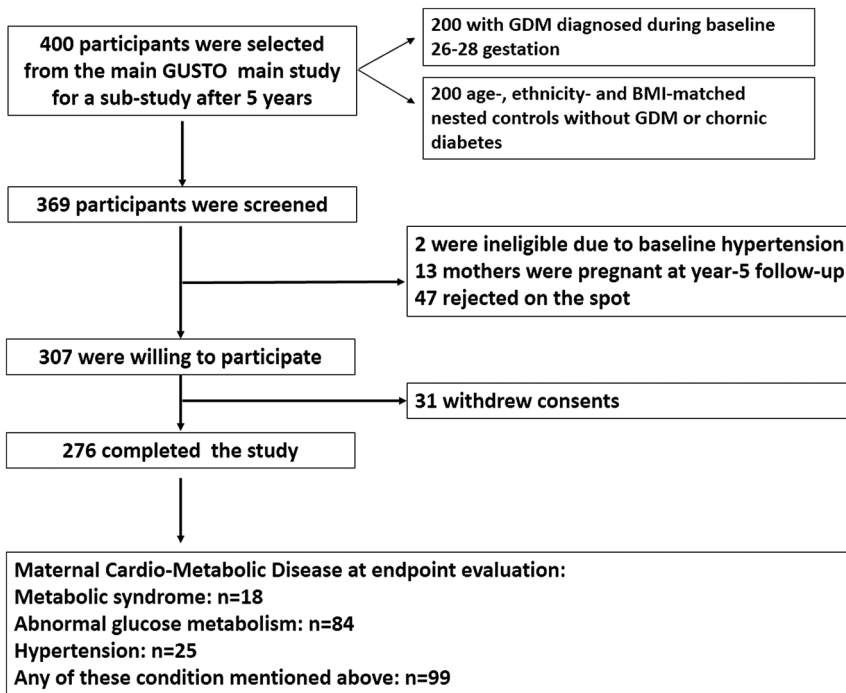
Figure 1

Flow chart of recruitment of our study of mothers.

Outcomes: maternal postpartum cardio-metabolic disease

All mothers underwent evaluation for metabolic outcomes. We measured blood pressure (BP), standing height and weight according to standardized protocols (19). We defined BMI as weight in kg/(height in m). We measured waist circumference using a standard measuring tape. Furthermore, we conducted venepuncture and sent serum samples to the Singapore General Hospital laboratory for a panel of blood tests, including levels of cholesterol (high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride (TG)), glycemic status (75 g oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1C) and insulin level) and C-reactive protein (CRP).

We applied Adults Treatment Panel (ATP) III 2000 to define postpartum MetS (21) when at least three of the four following components were met: (1) elevated BP: $SBP \geq 130$ mmHg and/or $DBP \geq 85$ mmHg or on anti-hypertensive medication; (2) abdominal obesity: waist circumference >88 cm; (3) dyslipidemia: $TG \geq 1.7$ mmol/L or HDL < 1.3 mmol/L and (4) glucose intolerance: fasting plasma glucose ≥ 6.1 mmol/L.

Furthermore, we defined following glucose abnormalities: (1) impaired fasting glucose (IFG) if fasting plasma glucose ranged between 6.1 mmol/L and 6.9 mmol/L (22); (2) impaired glucose tolerance (IGT) if fasting plasma glucose <7.0 mmol/L and 2-h plasma glucose between 7.9 and 11.0 mmol/L (22); (3) pre-diabetes

when either of the following present: IFG, IGT or HbA1C between 5.7 and 6.4% (23) and (4) type 2 diabetes (T2D) if fasting plasma glucose ≥ 7.0 mmol/L and/or 2-h plasma glucose ≥ 11.0 mmol/L (22). We grouped both diagnosis of pre-diabetes and T2D as abnormal glucose metabolism.

We defined postpartum HTN by following criteria: (1) mothers who were free from chronic HTN during baseline visit and (2) mothers' $SBP \geq 140$ mmHg and/or $DBP \geq 90$ mmHg at follow-up visit or currently on anti-hypertensive medication (24).

Other covariates

Trained staff administered questionnaires in English, Chinese, Malay or Tamil at follow-up visit. We collected information on maternal education, household income, family history of diabetes, parity, pre-pregnancy weight, smoking and alcohol drinking in the past one year and physical activity in the past three months. Weight gain between baseline and follow-up visits (5-year interval) were calculated as the difference of weight at follow-up visit and pre-pregnancy weight.

Statistical analysis

We calculated the mean and standard deviation (s.d.) or median and inter-quartile range (IQR) based on the distribution of continuous variables. We presented

baseline characteristics by postpartum cardio-metabolic diseases at follow-up visit: (1) MetS; (2) abnormal glucose metabolism; (3) HTN and (4) none of any of these cardio-metabolic diseases mentioned above.

We applied multiple linear regression models to examine the associations between GDM or HDP and postpartum cardio-metabolic risks. We log-transformed fasting plasma insulin, 2-h plasma insulin, HOMA-IR, triglyceride (TG) and CRP due to their skewed distributions and reported the exponentiated parameter estimates from linear regression associations. We further applied modified Poisson regression models to examine the associations of recurrent GDM, HDP with postpartum MetS, abnormal glucose metabolism and HTN diagnosed at follow-up visit. We also assessed the associations of co-existing GDM and HDP with postpartum cardio-metabolic diseases (defined as having postpartum MetS, abnormal glucose metabolism or HTN). We applied the following three models for both linear regression and modified Poisson regression analyses: Model 1-unadjusted; Model 2-adjusted for maternal age, ethnicity, college education and pre-pregnancy BMI; Model 3-Model 2 and additionally adjusted for cumulative parity.

To test the robustness of our study findings, we performed sensitivity analyses by including the following co-variables in Model 3: family history of diabetes, smoking history, alcohol consumption and weight gain during the 5-year interval. We investigated the potential effect modification using multiplicative interaction terms of ethnicity with either gestational complication. Statistical analyses were conducted using STATA (version 14.0, STATA, Texas, USA). We provided 95% confidence interval (CI) for all estimates and set a significant *P* value at 0.05.

Ethics approval statements

We conducted the study according to the tenets of the Declaration of Helsinki and obtained approval by the SingHealth Centralized Institutional Review Board and the National Health Group's Domain Specific Review Board. We obtained written informed consents from all participants at the 5-year follow-up visit.

Results

Among 276 mothers recruited in this study, there were 18 mothers (6.5%) diagnosed with MetS, 84 (30.4%) diagnosed with abnormal glucose metabolism, 25 (9.1%)

diagnosed with HTN and 99 (35.9%) diagnosed with any of these postpartum maternal cardio-metabolic diseases (Table 1). Of mothers with past GDM, 123 (44.6%) had only one GDM onset and 34 (12.3%) had at least two onsets. The remaining 119 mothers (43.1%) had no history of GDM. Of mothers with past HDP, 23 (8.3%) had one or more onsets of gestational HTN, PE or eclampsia (8.3%) (Table 1).

Mothers who developed MetS, abnormal glucose metabolism or HTN tended to be older in age (38.9 vs 37.8 vs 39.2 vs 32.9 years), have higher pre-pregnancy BMI (28.6 vs 25.7 vs 27.2 vs 22.8 kg/m^2), higher frequencies of reporting previous GDM or HDP and higher levels of cardio-metabolic risk measures including fasting glucose level, SBP, insulin level, waist circumference and lipid biomarkers, compared with mothers without development of any of the cardiometabolic diseases (Table 1).

Table 2 shows the associations of cumulative episodes of GDM and HDP with maternal cardio-metabolic risks in multiple linear regression models. After adjusting for maternal age, ethnicity, college education (yes vs no), pre-pregnancy BMI and parity, the number of previous GDM had associations with lower postpartum BMI, higher fasting and 2-h glucose levels in a dose–response pattern. For example, mothers with one GDM episode (−0.9 kg/m^2 (95% CI: −1.6, −0.1)) and at least two GDM episodes (−11.4 kg/m^2 (−2.5, −0.3)) were associated with lower postpartum BMI (*P*-trend <0.01), respectively. Mothers with prior GDM were associated with higher postpartum fasting glucose levels (one GDM episode: 1.05 mmol/L (1.0, 1.1); ≥2 GDM episodes: 1.07 mmol/L (1.0, 1.1), *P*-trend <0.001) and higher postpartum 2-h glucose levels (one GDM episode: 1.2 mmol/L (1.1, 1.3); ≥2 GDM episodes: 1.3 mmol/L (1.2, 1.4), *P*-trend <0.001). On the contrary, mothers with prior HDP were not associated with any of the metabolic risks measures, except for BP measures. Mothers with prior HDP were associated with both higher SBP (9.9 mmHg (4.3, 15.5)) and higher DBP (8.1 mmHg (3.7, 12.5)) (Table 2 and Supplementary Table 1, see section on supplementary data given at the end of this article).

We further applied modified Poisson regression model to assess the associations of cumulative GDM or HDP with individual postpartum cardio-metabolic diseases (Table 3). In the fully adjusted model, the relative risk (RR) (95% CI) of developing postpartum abnormal glucose metabolism was higher in mothers with ≥2 GDM episodes (RR=3.8 (2.1, 6.8)) than mothers with one episode of GDM (RR=2.9 (1.7, 4.8)), compared to mothers with no prior history of GDM (*P*-trend <0.001). Mothers with prior HDP were at

Table 1 Characteristics of participants with postpartum cardio-metabolic outcomes in our cohort of mothers (*n* = 276).

Characteristics	Postpartum MetS (*n* = 18)	Postpartum abnormal glucose metabolism (*n* = 84)	Postpartum HTN (*n* = 25)	Without any postpartum cardio-metabolic diseases (*n* = 177)
Maternal age, mean (S.D.) (years)	38.8 (5.6)	37.8 (4.9)	39.2 (4.9)	32.9 (4.8)
Ethnicity, *n* (%)				
Chinese (*n* = 152)	10 (6.6)	41 (27.0)	14 (9.2)	104 (68.4)
Malay (*n* = 60)	4 (6.7)	22 (36.7)	7 (11.7)	33 (55.0)
Indian (*n* = 64)	4 (6.3)	21 (32.8)	4 (6.3)	40 (62.5)
Maternal highest education, *n* (%)				
College and above (*n* = 158)	14 (8.9)	58 (36.7)	18 (11.4)	89 (56.3)
Below college (*n* = 118)	4 (3.4)	26 (22.0)	7 (5.9)	88 (74.6)
Household income, *n* (%)				
≥SGD 6000/month (*n* = 154)	14 (9.1)	54 (35.1)	20 (13.0)	88 (57.1)
<SGD 6000/month (*n* = 122)	4 (0.8)	30 (24.6)	5 (4.1)	89 (73.0)
Family history of DM, *n* (%)				
Yes (*n* = 123)	12 (9.8)	41 (33.3)	13 (10.6)	73 (59.3)
No (*n* = 153)	6 (4.0)	43 (35.2)	12 (7.8)	104 (68.0)
Pre-pregnancy BMI (kg/m²)	28.6 (2.8)	25.7 (5.1)	27.2 (4.1)	22.8 (4.2)
Cumulative episodes of GDM, *n* (%)				
Never (*n* = 119)	4 (3.4)	16 (13.4)	7 (5.9)	97 (81.5)
Once (*n* = 123)	12 (9.8)	52 (42.3)	15 (12.2)	64 (52.0)
Recurrent (≥2 times) (*n* = 34)	2 (5.9)	16 (47.1)	3 (8.8)	16 (47.1)
Cumulative episodes of HDP, *n* (%)				
Never (*n* = 253)	12 (4.7)	74 (29.2)	16 (6.3)	168 (66.4)
At least once (≥1 time) (*n* = 23)	6 (26.1)	10 (43.5)	9 (39.1)	9 (39.1)
Parity, *n* (%)				
One (*n* = 50)	2 (4.0)	17 (34.0)	4 (8.0)	32 (64.0)
Two (*n* = 130)	5 (3.8)	36 (27.7)	5 (3.8)	91 (70.0)
At least three (≥3) (*n* = 96)	11 (11.5)	31 (32.3)	16 (16.7)	54 (56.3)
OGTT				
Fasting glucose, mean (S.D.) (mmol/L)	5.5 (1.4)	5.3 (1.1)	5.1 (0.8)	4.7 (0.3)
2-h glucose, mean (S.D.) (mmol/L)	9.9 (3.3)	9.8 (2.6)	8.3 (3.4)	5.9 (1.0)
Insulin, median (IQR) (U/L)	11.8 (6.1)	8.9 (7.8)	8.5 (5.2)	5.7 (4.7)
HOMA-IR, median (IQR)	2.7 (1.8)	1.9 (2.0)	1.8 (1.2)	1.2 (1.0)
HbA1C, mean (S.D.) (%)	5.8 (0.7)	5.7 (0.7)	5.5 (0.4)	5.2 (0.3)
SBP, mean (S.D.) (mmHg)	131.7 (15.5)	116.6 (13.7)	137.2 (16.0)	109.9 (9.9)
DBP, mean (S.D.) (mmHg)	82.6 (11.6)	70.9 (11.0)	85.0 (11.6)	66.9 (8.2)
BMI (kg/m²)	30.4 (3.0)	27.6 (6.1)	28.1 (4.8)	24.5 (4.9)
Waist circumference (cm)	98.2 (7.8)	90.3 (13.0)	91.8 (12.2)	83.7 (10.8)
HDL, mean (S.D.) (mmol/L)	1.1 (0.2)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)
TG, median (IQR) (mmol/L)	1.4 (0.9)	1.2 (0.8)	1.4 (1.0)	0.8 (0.5)
CRP, median (IQR) (mg/L)	5.3 (7.0)	3.2 (7.6)	3.5 (6.0)	1.3 (2.7)
Weight gain[a], mean (S.D.) (kg)	7.14 (8.9)	5.8 (8.2)	4.1 (7.9)	5.7 (8.1)

[a]Weight gain = (weight at follow-up visit) − (pre-pregnancy BMI).
BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; HTN, hypertension; IQR, inter-quartile range; MetS, metabolic syndrome; SBP, systolic blood pressure; S.D., standard deviation; TG, triglyceride.

an increased risk of developing postpartum MetS (RR = 5.5 (2.3, 13.3)) and postpartum HTN (RR = 6.2 (3.1, 12.4)) in the unadjusted model. However, only the association with postpartum HTN remained significant after adjusting for maternal age, ethnicity, college degree, pre-pregnancy BMI and parity (RR = 3.6 (1.5, 8.6)) (Table 3).

To assess the associations of either or combined GDM and HDP complications with postpartum cardio-metabolic diseases, we further applied modified Poisson regression models with any of the cardio-metabolic diseases as the outcome variable. In a fully adjusted model, mothers with either or both of these conditions were associated with an increased risk of developing any of the cardio-metabolic diseases after delivery (RR = 2.6 (1.7, 3.9) and RR = 2.7 (1.6, 4.9), respectively) compared to mothers with neither GDM nor HDP (Table 4). These estimates and the 95% CIs did not show increment between having either single and having combined complications in the past (Table 4).

Additional adjustment for maternal characteristics (e.g. family history of diabetes, smoking history and

Table 2 Associations of cumulative episodes of gestational diabetes and hypertensive disorders with postpartum maternal cardio-metabolic risks assessment (Multiple linear regression models).

Cumulative major gestational complications		SBP (mmHg)	DBP (mmHg)	BMI (kg/m²)	Waist circum (cm)	Exp (log₁₀ fasting glucose) (mmol/L)	Exp (log₁₀ 2-h glucose) (mmol/L)	Exp (log₁₀ insulin) (U/L)	Exp (log₁₀ HOMA) (units)	Exp (log₁₀ TG) (mmol/L)	HDL (mmol/L)	Exp (log₁₀ CRP) (mg/L)
Postpartum cardio-metabolic risks assessment, β (95% CI)												
Cumulative GDM												
Never	Model 1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once		0.5 (−2.9, 3.9)	0.4 (−2.2, 2.9)	0.7 (−0.7, 2.1)	1.3 (−1.7, 4.3)	**1.07 (1.0, 1.1)**	**1.3 (1.2, 1.4)**	**1.2 (1.0, 1.4)**	**1.3 (1.1, 1.5)**	1.1 (0.95, 1.2)	−0.1 (−0.1, 0.01)	1.3 (0.3, 1.8)
Recurrent (≥2)		2.1 (−3.1, 7.2)	1.5 (−2.3, 5.4)	−1.0 (−3.1, 1.1)	−1.8 (−6.3, 2.8)	**1.07 (1.0, 1.1)**	**1.3 (1.2, 1.5)**	1.0 (0.8, 1.3)	1.1 (0.8, 1.4)	0.9 (0.8, 1.1)	−0.1 (−0.2, 0.1)	1.2 (0.7, 1.9)
Never	Model 2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once		−1.2 (−4.5, 2.1)	−1.1 (−3.7, 1.5)	**−0.9 (−1.6, −0.1)**	**−2.1 (−4.1, −0.04)**	**1.05 (1.0, 1.1)**	**1.2 (1.2, 1.3)**	1.05 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	−0.02 (−0.09, 0.06)	1.0 (0.8, 1.4)
Recurrent (≥2)		2.1 (−2.8, 7.0)	1.3 (−2.5, 5.1)	**−1.4 (−2.5, −0.3)**	−2.6 (−5.6, 0.4)	**1.07 (1.0, 1.1)**	**1.3 (1.2, 1.4)**	1.0 (0.8, 1.2)	1.05 (0.9, 1.3)	0.9 (0.7, 1.1)	−0.06 (−0.16, 0.05)	1.1 (0.7, 1.7)
Never	Model 3	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Once		−1.2 (−4.5, 2.1)	−1.3 (−3.9, 1.3)	**−0.9 (−1.6, −1.0)**	−1.9 (−4.0, 0.1)	**1.05 (1.0, 1.1)**	**1.2 (1.1, 1.3)**	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	1.0 (0.91, 1.1)	−0.02 (−0.09, 0.06)	1.1 (0.8, 1.4)
Recurrent (≥2)		1.6 (−3.4, 6.7)	1.3 (−2.6, 5.3)	**−1.3 (−2.5, −0.2)**	−2.6 (−5.7, 0.5)	**1.07 (1.0, 1.1)**	**1.3 (1.2, 1.4)**	1.0 (0.9, 1.3)	1.1 (0.9, 1.4)	0.9 (0.8, 1.1)	−0.05 (−0.16, 0.06)	1.2 (0.8, 1.8)
P-trend				**<0.001**		**<0.0001***	**<0.001***					
Cumulative HDP												
Never	Model 1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
At least once (≥1)		**12.6 (7.1, 18.2)**	**9.0 (4.8, 13.2)**	**3.0 (0.7, 5.3)**	**6.3 (1.2, 11.3)**	1.0 (0.98, 1.1)	**1.11 (1.0, 1.3)**	1.1 (0.9, 1.5)	1.2 (0.9, 1.6)	**1.2 (1.0, 1.5)**	−0.1 (−0.2, 0.1)	**1.7 (1.0, 3.0)**
Never	Model 2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
At least once (≥1)		**9.8 (4.3, 15.3)**	**7.5 (3.2, 11.8)**	0.4 (−0.9, 1.7)	1.3 (−2.2, 4.9)	1.0 (0.95, 1.1)	1.1 (0.93, 1.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	−0.1 (−0.2, 0.1)	1.5 (0.9, 2.4)
Never	Model 3	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
At least once (≥1)		**9.9 (4.3, 15.5)**	**8.1 (3.7, 12.5)**	0.4 (−1.0, 1.7)	1.0 (−2.6, 4.5)	1.0 (0.95, 1.1)	1.1 (0.93, 1.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	−0.1 (−0.2, 0.05)	1.4 (0.9, 2.2)

Model 1, unadjusted; Model 2, adjusted for mom age at enrolment, maternal ethnicity, maternal college education, and pre-pregnancy BMI; Model 3, Model 2+cumulative parity.
*P-trend is based on log10 transform estimates.

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; SBP, systolic blood pressure; TG, triglyceride; waist circum, waist circumference.

Table 3 Associations of cumulative episodes of gestational diabetes mellitus and hypertensive disorders with postpartum cardio-metabolic diseases (modified Poisson regression models).

Cumulative gestational complications collected at year 5 follow-up visit		RR (95% CI)		
		Postpartum MetS Yes (*n* = 18)	Postpartum glucose abnormality Yes (*n* = 84)	Postpartum HTN Yes (*n* = 25)
Cumulative GDM				
Never	Model 1	Reference	Reference	Reference
Once		**2.9 (1.0, 8.8)**	**3.1 (1.9, 5.2)**	2.1 (0.9, 4.9)
Recurrent (≥2)		1.8 (0.3, 9.2)	**3.5 (2.0, 6.2)**	1.5 (0.4, 5.5)
Never	Model 2	Reference	Reference	Reference
Once		1.7 (0.6, 5.0)	**2.9 (1.7, 4.8)**	1.5 (0.6, 3.8)
Recurrent (≥2)		1.6 (0.3, 8.6)	**3.5 (2.0, 6.1)**	1.3 (0.4, 4.9)
Never	Model 3	Reference	Reference	Reference
Once		1.7 (0.5, 5.5)	**2.9 (1.7, 4.8)**	1.6 (0.6, 4.1)
Recurrent (≥2)		1.1 (0.2, 5.7)	**3.8 (2.1, 6.8)**	0.9 (0.2, 3.3)
			***P*-trend <0.001**	
Cumulative HDP				
Never	Model 1	Reference	Reference	Reference
At least once (≥1)		**5.5 (2.3, 13.3)**	1.5 (0.9, 2.5)	**6.2 (3.1, 12.4)**
Never	Model 2	Reference	Reference	Reference
At least once (≥1)		2.8 (0.8, 9.9)	1.1 (0.7, 1.9)	**4.4 (1.9, 10.6)**
Never	Model 3	Reference	Reference	Reference
At least once (≥1)		2.8 (0.8, 9.9)	1.1 (0.7, 1.9)	**3.6 (1.5, 8.6)**

Model 1, unadjusted; Model 2, adjusted for mom age at enrolment, maternal ethnicity, maternal college education, and pre-pregnancy BMI; Model 3, Model 2 + cumulative parity.
CI, confidence interval; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; HTN, hypertension; MetS, metabolic syndrome; RR, relative risk.

weight gain between baseline recruitment and 5-year follow-up visit) did not appreciably change the associations observed. We found no evidence of effect modification by maternal ethnicity (*P*-value in all interactions >0.05) on the reported associations.

Discussion

In this cohort of mothers with and without GDM (~1:1 ratio) at baseline, we found significant associations between the increased episodes of GDM and increased risk of postpartum abnormal glucose metabolism in a dose–response pattern and between HDP and the risk of postpartum HTN. Furthermore, mothers having either or both GDM and HDP in the past were at significantly higher risk of any postpartum cardio-metabolic diseases than mothers with neither gestational complications. However, no synergic effect of co-existing GDM and HDP on the risk of cardio-metabolic diseases was evident.

There is still paucity of studies assessing the effect of recurrent GDM on the development of postpartum cardio-metabolic diseases (17). A study conducted on a large population of women with prior GDM found a significant dose–response association between numbers of pregnancies with GDM and incident renal morbidity

after 11.2-year follow-up (13). The authors suggested that women with more episodes of GDM exhibited lower levels of plasma adiponectin, higher degrees of carotid intimal-medial thickness and subclinical inflammation, and thus, persistent generalized vascular dysfunction compared to women without or with fewer episodes of GDM (13). Conversely, a recent study of 72 mothers (41 with one episode of GDM, 21 with recurrent GDM, 10 healthy controls) yielded no evidence supporting a harmful effect of recurrent GDM on the 5-year deterioration of glucose metabolism, insulin sensitivity and secretion, nor on increased cardiovascular risks (25). The authors reported comparable degrees of weight retention after pregnancy and metabolic deterioration in both recurrent GDM and non-recurrent GDM groups (25). Some authors believed that impaired glucose tolerance and worsening insulin resistance were not caused by cumulative episodes of GDM in live births, but by the mother's weight retention entering the next pregnancy (26). Other researchers suggested that women prior to GDM could have modified their lifestyle between pregnancies or during their second pregnancy, resulting in weight loss or reduced weight gain during pregnancy, improved nutrition consumption and/or increased physical activity (27). Therefore, the risk of progression toward postpartum T2D might not be in a linear pattern, especially when observation was over short

Table 4 Associations of individual or combined two major gestational complications (GDM and HDP) with any postpartum maternal cardio-metabolic diseases (modified Poisson regression models).

Gestational major complications		Any postpartum cardio-metabolic disease Yes (*n* = 99) RR (95% CI)
Without either major gestational complications (*n* = 115)	Model 1	Reference
With either major gestational complications (*n* = 142)		**2.7 (1.8, 4.2)**
With Both major gestational complications (*n* = 19)		**3.6 (2.1, 6.2)**
Without either major gestational complications (*n* = 115)	Model 2	Reference
With either major gestational complications (*n* = 142)		**2.5 (1.7, 3.9)**
With Both major gestational complications (*n* = 19)		**2.9 (1.7, 5.1)**
Without either major gestational complications (*n* = 115)	Model 3	Reference
With either major gestational complications (*n* = 142)		**2.6 (1.7, 3.9)**
With Both major gestational complications (*n* = 19)		**2.7 (1.6, 4.9)**
		P-trend <0.001

Model 1, unadjusted; Model 2, adjusted for mom age at enrolment, maternal ethnicity, maternal college education, and pre-pregnancy BMI; Model 3, Model 2+cumulative parity.
CI, confidence interval; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; HTN, hypertension; MetS, metabolic syndrome; RR, relative risk.

periods of time. The significant dose–response association between episodes of GDM and postpartum abnormal glucose tolerance in our study is in accordance with Beharier and coworkers (13), even after we adjusted for weight gain during a 5-year interval for model robustness testing. We agreed with Beharier and coworkers that mothers with more than one episode of GDM in all live births represented a higher degree of insulin resistance and β-cell dysfunction, which more likely resulted in pre-diabetes and diabetes than mothers without or only one episode of GDM.

GDM and HDP are two major common pregnancy complications throughout pregnancy (1, 2, 3). Women with GDM were more prone to insulin resistance later in life, which underlies the development of metabolic disorders such as MetS, pre-diabetes and T2D (6, 10, 16, 28, 29). Women with HDP – mainly gestational hypertension and preeclampsia – were more susceptible to prolonged vascular endothelial dysfunction (30, 31) or cardiovascular outcomes including hypertension and cardiovascular diseases later in life (3). Even though GDM and HDP may appear to be unrelated, due to their distinctly different clinical manifestation and diagnostic criteria, researchers speculate that glucose intolerance might affect vascular dysfunction and vice versa (18, 30, 32). Furthermore, both gestational complications share common risk factors such as maternal age, parity and pre-pregnancy BMI, that could imply that they may also share pathophysiological changes predisposing to subsequent recurrence of pregnancy complications and postpartum cardio-metabolic disorders over the long term (18, 32). However, our findings from this study sample do not support GDM and HDP sharing risks for postpartum

glucose metabolism disorders or HTN. We found that mothers with prior GDM were at risk of deterioration of glucose metabolism including fasting and 2-h glucose level and development of pre-diabetes and T2D, yet not at risk of CVD risks including CRP, BP, high cholesterol or development of MetS or HTN. Similarly, mothers with prior HDP were only at risk of development of postpartum HTN, and peripheral vascular resistance including SBP and DBP, yet not at the risk of any metabolic risks. In addition, we observed that mothers with either or combined history of GDM and HDP had similar magnitude of increased risks of developing any cardio-metabolic disease than mothers with neither gestational complication. Even though it is well known that GDM and HDP identify women at high vascular risk, we did not observe a synergistic effect of co-existing pregnancy complications on the risk of developing any cardio-metabolic diseases. This might be attributed to a small sample size, which lacks statistical power to detect different effect sizes between individual and combined GDM and HDP groups. Future studies with either a longer follow-up period or a larger sample size, are therefore warranted to address this issue.

The strength of our study includes a prospective study design and a reasonable response rate (78%). Detailed information on pregnancy, birth outcomes and detailed past history of all episodes of GDM and HDP were collected in a chronological sequence. Maternal postpartum cardio-metabolic diseases including MetS, abnormal glucose metabolism and HTN were diagnosed according to standard WHO or ATP guidelines. All cardio-metabolic risk assessments followed standardized protocols. However, there are limitations that one should bear in mind when interpreting our findings. First, baseline GDM diagnosis

was defined by WHO 1999 guidelines, which only requires fasting and 2-h glucose testing after a 75 g oral glucose intake. As it has been suggested that IADSPG criteria may be more sensitive in identifying mild glucose intolerance during pregnancy, GDM cases may be misclassified. Second, even though we have calculated weight gain or weight retention between baseline and 5-year follow-up, we were not able to collect detailed weight gain after each pregnancy from each mother. The rough estimation of weight retention might not be accurate. Third, our samples were purposely selected with 1:1 ratio of mothers with and without GDM at baseline, and therefore, the estimated magnitudes of relative risks may restrict the generalizability of our findings to the general pregnant women population where the prevalence of GDM is much less than 50%. Fourth, our data on history of GDM and HDP were based on self-reports, and we could not collect accurate information on medication history for both GDM and HDP during pregnancy. Therefore, recall bias and residual confounding (e.g. medication due to GDM and/or HDP during pregnancy) may have potentially affected our study findings. Finally, as some mothers with an episode of GDM and/or HDP did not or were not able to conceive subsequently, our findings could have underestimated the risks under investigation.

Conclusion

In summary, this study shows evidence of an individual yet not synergic contribution of GDM and HDP to the risk of postpartum cardio-metabolic diseases. Our findings suggest that GDM and HDP represent distinctly different pathogeneses during pregnancy and are associated with increased risk of different cardio-metabolic diseases later in life, without evidence of synergy.

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