In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring

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OBJECTIVE

The objective of this study was to evaluate the effect of maternal hyperglycemia during pregnancy on cardiometabolic risk in offspring during early childhood.

RESEARCH DESIGN AND METHODS

A total of 970 mothers who had joined the Hyperglycemia and Adverse Pregnancy Outcome study were reevaluated, together with their child born during the study period, 7 years after delivery.

RESULTS

Offspring born to mothers diagnosed with gestational diabetes mellitus (GDM), as defined by the World Health Organization 2013 GDM criteria, had higher rates of abnormal glucose tolerance (4.7% vs. 1.7%; *P* = 0.04), higher rates of overweight or obesity, greater BMI, higher blood pressure (BP), lower oral disposition index, and a trend toward reduced β-cell function compared with those born to mothers without GDM. For each SD increase in maternal fasting, 1-h, and 2-h glucose levels on oral glucose tolerance tests (OGTTs) between 24 and 32 weeks of the index pregnancy, the risk of abnormal glucose tolerance in the offspring showed a corresponding increase (adjusted odds ratio [OR] 1.85–2.00). The associations were independent of BMI before pregnancy, childhood obesity, or being born large for gestational age. The area under the curve for glucose levels during the five-point OGTT increased to a similar extent in boys and girls with each SD increase in maternal 1-h and 2-h plasma glucose on OGTTs during pregnancy. All three maternal glucose levels were also associated with increased adjusted ORs for childhood overweight or obesity and adiposity among girls, but not boys.

CONCLUSIONS

Maternal hyperglycemia in pregnancy is independently associated with offsprings' risk of abnormal glucose tolerance, obesity, and higher BP at 7 years of age. Its effect on childhood adiposity was apparent only in girls, not boys.

The U.S. Preventive Services Task Force recently approved universal gestational diabetes mellitus (GDM) screening as a preventive measure for type 2 diabetes mellitus (DM) (1). This policy may be more justifiable if the identification of maternal GDM can also help to reduce long-term metabolic consequences among offspring. However, the follow-up analyses of both the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal-Fetal Medicine Units (MFMU)

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trials failed to show a reduction in childhood obesity and glucose intolerance with antenatal glycemic treatment administered to mothers (2,3). Nevertheless, neither trial was powered to address long-term metabolic consequences in offspring.

The association of in utero hyperglycemia with fetal programming was first described in the Native American Pima population, among whom is found a high prevalence of obesity, type 2 DM, and GDM. Offspring born to mothers who had DM during pregnancy had a considerably higher risk of DM and obesity than those born to mothers who developed DM after pregnancy (4,5). Similarly, offspring exposed to maternal DM during gestation had a higher risk of DM than their siblings born before the onset of DM in the mother, after eliminating confounding effects of genetic variation and similar lifestyle characteristics (6). However, whether similar putative programming effects occur in mild maternal hyperglycemia in other populations remains uncertain. Earlier studies that examined the risk association between maternal GDM and susceptibility to DM in the offspring were limited by their retrospective designs and lack of control groups (7–9). More than 10 prospective cohort studies have reported the effects of maternal GDM on offsprings' risks of obesity or glucose tolerance, with inconsistent results, in part because of differences in the definitions of maternal hyperglycemia and GDM and in adjustments for confounding factors (10–21). Importantly, all mothers diagnosed with GDM had inevitably received interventions to normalize the glycemic level during pregnancy, except in one study (17,18). Furthermore, postnatal education regarding and investigation for maternal GDM during repeat follow-up visits also confounded the data interpretation and conclusions. While many experts reckon that exposure to in utero hyperglycemia will increase the future risk of obesity and type 2 DM in offspring, others argue that the apparent risk association might be explained by confounding factors (22).

In this study we examined the effect of maternal hyperglycemia on childhood cardiometabolic health in offspring born to a cohort of women in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. Mothers in this cohort had never received any prior antenatal or postnatal intervention, and their glycemic status at the index pregnancy remained undisclosed.

RESEARCH DESIGN AND METHODS

Participants

The participants were mothers who were ethnic Chinese seen at the Hong Kong study center from the original HAPO study, along with their children born from the index pregnancy. Details of the HAPO study have been described previously (23). All women underwent a standard 75-g oral glucose tolerance test (OGTT) between 24 and 32 weeks of gestation. Data concerning smoking and alcohol use, history of DM and hypertension among first-degree relatives, and demographic characteristics were collected using standardized questionnaires (23). Blood was collected between 34 and 37 weeks of gestation for the evaluation of random plasma glucose (PG) levels, as a safety measure to identify women with hyperglycemia above a predefined threshold. The OGTT results were unblinded if the 2-h PG level was diagnostic of DM (i.e., $>$11.1 mmol/L), the fasting PG level exceeded 5.8 mmol/L, the random PG level at 34–37 weeks' gestation was $\geq$8.9 mmol/L, or any PG level was $<$2.5 mmol/L. Eligible subjects were invited to attend a follow-up assessment at the Prince of Wales Hospital between 2009 and 2013. Non-Chinese women and those whose OGTT results were unblinded for the above reasons were excluded from the study.

Study Procedures

Both the mother and her child were scheduled for a follow-up visit in the morning, after at least 8 h of fasting, when the child was around 7 years of age. Assessments were rescheduled for mothers who were pregnant or if either the mother or the child had an acute illness at the time of the visit. Research staff explained the study objective and procedures to both the mother and the child, and written informed consent was obtained from parents or legal guardians. The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Demographic Data

Demographic data on personal medical history, family history, dietary habits, and physical activity were collected using structured questionnaires. The children's physical activity was assessed by the Chinese University of Hong Kong: Physical Activity Rating for Children and Youth, which is a one-item activity rating modified from the Jackson Activity Coding and the Godin-Shephard Activity Questionnaire for adolescents (24,25). This rating adopted an 11-point score to grade levels of physical activity, ranging from no exercise at all (0) to vigorous exercise on most days (10), taking into consideration the frequency, duration, and intensity of activity.

Standing height without shoes was measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain Ltd., Crymych, U.K.); body weight (with light clothing) was measured to the nearest 0.1 kg (Tanita physician digital scale, model no. TBF 410; Tanita Corp., Tokyo, Japan). Waist circumference, at the midpoint between the lower ridge of the ribs and the top of the iliac crest, was measured to the nearest 0.1 cm using a nonelastic flexible tape. Hip circumference was measured at the broadest circumference below the waist. We measured skinfold thickness at four sites on the right side (biceps, triceps, subscapular, and suprailiac) using a Holtain Tanner/Whitehouse skinfold caliper (Holtain Ltd.). Blood pressure (BP) was measured three times in the nondominant arm using an Omron T5 BP monitor (Omron Healthcare Co. Ltd., Kyoto, Japan), at 1-min intervals, after 5 min of rest. The mean readings were used for analysis. All subjects were advised to abstain from smoking and drinking alcohol, tea, or coffee on the day before the follow-up evaluation.

Biochemical Tests

All mothers underwent a 75-g OGTT at two time points, unless they were treated with antidiabetes drugs. Children had an OGTT at five time points after receiving a glucose load of 1.75 g/kg body weight, or a 75-g glucose load if they weighed $\geq$42.8 kg. Venous blood samples were collected at baseline (fasting) and at 15, 30, 60, and 120 min following the glucose load and used to measure PG and insulin. Fasting blood was also collected to determine C-peptide levels, lipid profile, and renal and liver function. If the child could not complete the OGTT or vomited during

the procedure, the test was discontinued and not repeated.

PG was measured with the hexokinase method, using an automated analyzer (Hitachi 911; Boehringer Mannheim, Mannheim, Germany). Both the intra- and interassay coefficients of variation for glucose were 2% at 6.6 mmol/L. Plasma insulin and C-peptide levels were analyzed using an immunoassay analyzer (Immulite 1000 Immunoassay System; Siemens, Munich, Germany), with the lowest detection limits at 2.0 mIU/L and 0.1 μg/L, respectively. The interassay coefficients of variation for insulin were 4.8% and 4.4% at 9.8 and 45.4 mIU/L, respectively; those for C-peptide were 3.6%, 3.1%, and 4.5% at 0.68, 3.0, and 6.7 μg/L, respectively. Plasma triglyceride and both HDL and LDL cholesterol levels were measured with enzymatic methods, using a DP Modular Analytics system (Roche Diagnostics, Indianapolis, IN).

Outcome Measures

The primary outcome was the rate of abnormal glucose tolerance in the offspring of mothers retrospectively classified as having GDM based on the latest World Health Organization definition (26). The secondary outcomes included offsprings' insulin sensitivity, pancreatic β-cell function, oral disposition indices, BMI, BP, overweight or obesity, adiposity, and prehypertension and hypertension status. We defined DM, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) according to the American Diabetes Association diagnostic criteria. Abnormal glucose tolerance was defined as the presence of IFG, IGT, or DM. Insulin sensitivity was calculated using the Matsuda insulin sensitivity index (ISI) (27). Pancreatic β-cell function was determined using the formula AUC(I) (pmol/L) ÷ AUC(G) (mmol/L) (28), where AUC(I) and AUC(G) are the area under the plasma insulin level–time curve and the PG level–time curve, respectively, from 0 to 120 min in the OGTT; the HOMA of β-cell function also was used to assess pancreatic β-cell function (29). The insulinogenic index, a surrogate for first-phase insulin secretion, of the OGTT was estimated using the formula $[(I^{30} - I^{0})$ (pmol/L) ÷ $(G^{30} - G^{0})$ (mmol/L)] (30), where G^{0} and G^{30} are the fasting and 30-min PG levels, and I^{0} and I^{30} are the fasting and 30-min insulin levels, respectively. The oral disposition index, which assesses the acute insulin response in relation to the level of insulin sensitivity, was defined as $(I^{30} - I^{0})$ (mIU/L) ÷ $(G^{30} - G^{0})$ (mg/dL) × Matsuda ISI (31).

Obesity (BMI ≥95th percentile) and overweight (BMI ≥85th to <95th percentiles) were defined according the Centers for Disease Control and Prevention on the basis of age- and sex-specific BMI percentiles for the local Chinese population (32). Adiposity was defined as the sum of skinfold thickness (at four sites) at or above the 90th percentile, whereas prehypertension and hypertension were defined according to the age-, sex-, and height-specific reference ranges from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (30).

Statistical Analysis

Data are expressed as mean ± SD or counts with proportions. Between-group differences were compared using the Student *t* test and the χ^2/Fisher exact tests, as appropriate. Univariable and multivariable linear regression analyses were used to assess the associations between continuous variables. Multivariable logistic regression analysis was used to obtain adjusted odds ratios (ORs) with 95% CIs, with the forced entry of potential confounders. Plasma insulin and C-peptide levels below the detection limits were corrected to the lowest detectable levels. All statistical analyses were performed in SPSS version 22 (SPSS, Chicago, IL). *P* values <0.05

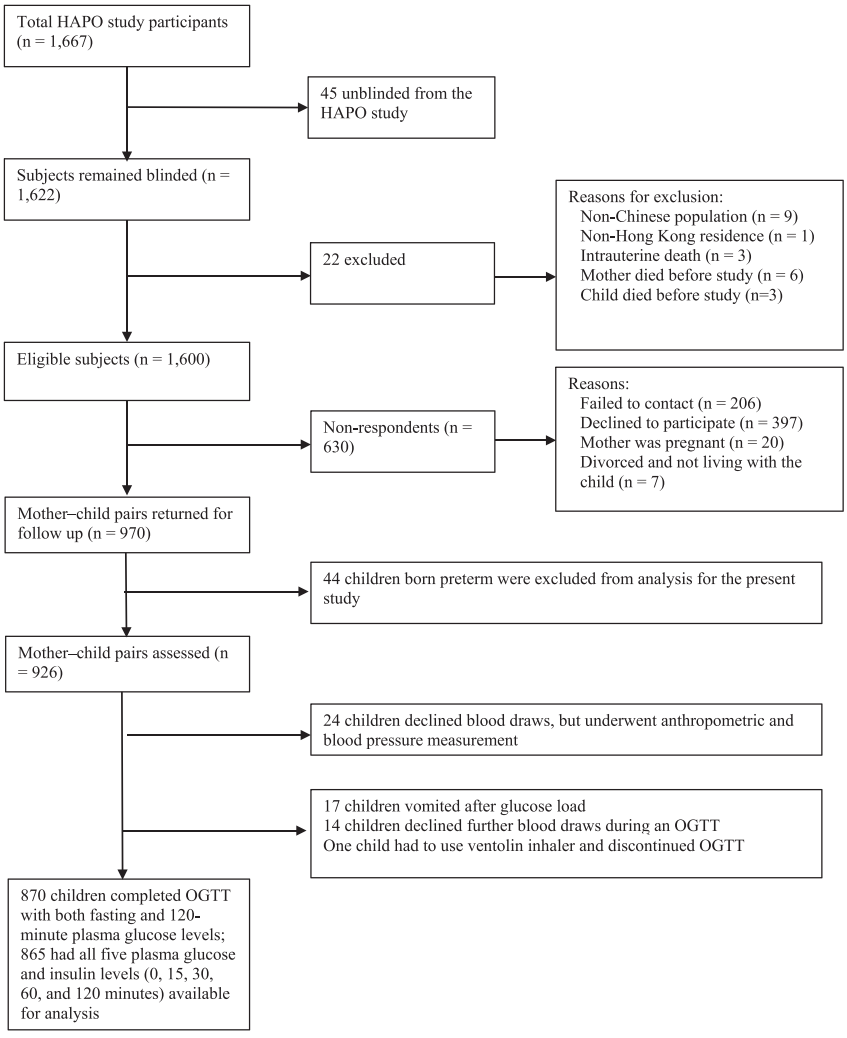

Figure 1—Flowchart of HAPO study participants from the Hong Kong field center and eligible subjects in the follow-up study.

were used to indicate significance for two-tailed statistical test results. There is no epidemiological data of childhood abnormal glucose tolerance in our population. Assuming maternal GDM increases in prevalence from a background rate of 1% to 4%, 1,532 subjects are required to obtain a power of 80% at a 5% significance level.

RESULTS

A total of 970 eligible mother-child pairs (60.6%) returned for a follow-up assessment. Blood was successfully collected from 902 children, of whom 96% completed sampling at five time points (Fig. 1). Mothers who returned for follow-up were older and more commonly affected by GDM at the index pregnancy, whereas their children had higher C-peptide levels in cord blood serum at birth.

Mothers who had GDM during the index pregnancy were older and had a higher BMI before pregnancy compared with their peers with normal glucose tolerance; they also had a higher rate of DM and prediabetes at the time of follow-up (Supplementary Table 1). Their children were also heavier and had greater adiposity and higher C-peptide levels in umbilical cord blood at delivery.

Compared with the children of mothers without GDM, the 7-year-old offspring of mothers with GDM (OGDM) had higher 30- and 60-min PG levels, larger AUC(G) at the OGTT, higher rates of abnormal glucose tolerance, lower oral disposition indices, and a trend toward lower insulinogenic indices at 30 min (Table 1). The OGDM also had higher BMI, a higher rate of overweight or obesity, and a higher BP, but there was no difference in the rates of prehypertension or hypertension compared with their peers born to mothers without GDM. Higher rates of overweight or obesity and adiposity were only observed among girls, not boys, among OGDM, whereas a higher AUC(G) was observed for both sexes. There were no significant differences in the history of breastfeeding, dietary habits, and exercise levels between the two groups.

Table 2 shows the associations of maternal glycemia (fasting, 1-h, and 2-h PG levels during the OGTT in the index pregnancy) with the offsprings' cardiometabolic risk factors. The adjusted ORs of abnormal glucose tolerance in offspring increased by 1.85–2.00 with every 1-SD increase for all three maternal glycemic levels. In addition, every 1-SD increase in maternal glycemic levels was associated with an increase in the odds of

Table 1—Characteristics and cardiometabolic outcomes at 7 years of age between the offspring of mothers with normal glucose tolerance and mothers with GDM

	Offspring		
	Mothers with NGT (n = 794)	Mothers with GDM (n = 132)	P value
Anthropometry			
Children's age (years), median (interquartile range)	7.0 (6.7–7.2)	6.9 (6.6–7.2)	0.03
BMI (kg/m^2)*	15.0 ± 2.3	15.3 ± 2.1	0.04
BMI percentile	42.6 ± 31.1	50.9 ± 32.0	0.01
Obesity (BMI ≥95th percentile)	67 (8.4)	9 (6.8)	0.53
Overweight or obesity (BMI ≥85th percentile)			
Overall	121 (15.3)	30 (22.7)	0.03
Boys	73 (17.2)	13 (22.8)	0.30
Girls	48 (13.0)	17 (22.7)	0.03
Waist-to-hip ratio*	0.84 ± 0.05	0.84 ± 0.04	0.64
Sum of skinfold thickness (mm)*			
Overall	35.8 ± 17.4	38.7 ± 15.7	0.07
Boys	35.2 ± 18.2	35.6 ± 15.4	0.71
Girls	36.4 ± 16.5	41.0 ± 15.5	0.03
Glycemia and insulin			
PG (mmol/L)			
Fasting	4.57 ± 0.35	4.64 ± 0.49	0.12
15 min	7.03 ± 1.16	7.20 ± 1.30	0.14
30 min	7.54 ± 1.49	7.99 ± 1.58	0.002
60 min	5.87 ± 1.51	6.30 ± 1.66	0.004
120 min	5.29 ± 0.97	5.39 ± 0.96	0.26
AUC(G)			
Overall	732 ± 118	768 ± 121	0.002
Boys	731 ± 118	769 ± 115	0.03
Girls	734 ± 119	766 ± 127	0.04
Children's glycemic status†			
IFG and/or IGT	13 (1.7)	5 (3.9)	0.04
DM	0 (0)	1 (0.8)	0.04
Fasting plasma insulin (mIU/L)	4.07 ± 5.33	3.77 ± 3.57	0.53
Fasting C-peptide (μg/L)	0.38 ± 0.43	0.32 ± 0.37	0.14
Matsuda ISI	16.2 ± 8.9	15.0 ± 8.3	0.14
HOMA-BCF	77.6 ± 72.8	71.4 ± 65.2	0.38
Insulinogenic index at 30 min	81.0 ± 94.2	67.8 ± 65.0	0.05
Oral disposition index	7.98 ± 9.43	6.62 ± 5.95	0.04
Lipid profile			
Total cholesterol (mmol/L)	4.47 ± 0.74	4.52 ± 0.68	0.41
HDL cholesterol (mmol/L)	1.66 ± 0.35	1.65 ± 0.31	0.73
LDL cholesterol (mmol/L)	2.47 ± 0.64	2.53 ± 0.61	0.33
Triglyceride (mmol/L)	0.74 ± 0.33	0.78 ± 0.34	0.24
Dyslipidemia‡	63 (8.2)	11 (8.4)	0.94
BP (mmHg)			
SBP*	102 ± 8.9	104 ± 8.7	0.01
DBP*	62 ± 7.9	63 ± 8.1	0.06
SBP at age-, sex-, and height-specific percentile	60 ± 24	66 ± 22	0.01
DBP at age-, sex-, and height-specific percentile	60 ± 22	64 ± 22	0.02
Hypertension (BP ≥95th percentile)	63 (8.0)	11 (8.3)	0.89
Prehypertension (BP 90th to <95th percentile)	50 (6.3)	11 (8.3)	0.51

Data are mean ± SD or n (%), unless otherwise indicated. BCF, β-cell function; DBP, diastolic blood pressure; NGT, normal glucose tolerance; SBP, systolic blood pressure. *Between-group comparison by ANCOVA after adjustment for age and/or sex as appropriate. †χ^2 test based on the rate of abnormal glucose tolerance. ‡Triglyceride ≥1.7 mmol/L or LDL cholesterol ≥3.4 mmol/L.

Table 2—Unadjusted and adjusted ORs for associations between maternal glycemic level during pregnancy and offsprings' cardiometabolic characteristics at 7 years of age

	Maternal fasting PG		Maternal 1-h PG		Maternal 2-h PG		GDM	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Abnormal glucose tolerance*								
Overall	1.86 (1.24–2.77)‡	1.85 (1.20–2.86)‡	1.81 (1.15–2.85)†	1.95 (1.18–3.22)‡	1.76 (1.15–2.69)‡	2.00 (1.21–3.31)‡	2.90 (1.08–7.77)†	3.08 (1.04–9.13)†
Boys	1.71 (1.02–2.89)†	1.68 (0.95–2.98)	1.79 (1.02–3.13)†	1.82 (0.95–3.47)	1.86 (1.05–3.31)†	1.82 (0.92–3.58)	4.17 (1.21–14.38)†	3.89 (0.96–15.81)
Girls	2.12 (1.12–4.02)†	2.56 (1.16–5.68) †	1.96 (0.89–4.30)	2.47 (0.98–6.18)	1.75 (0.91–3.37)	2.04 (0.98–4.26)	1.95 (0.37–10.28)	2.34 (0.41–13.50)
Overweight or obesity (BMI ≥85th percentile)§								
Overall	1.15 (0.97–1.37)	1.11 (0.92–1.34)	1.28 (1.07–1.52)‡	1.26 (1.04–1.53)†	1.24 (1.04–1.47)†	1.25 (1.03–1.51)†	1.63 (1.04–2.56)†	1.59 (0.97–2.59)
Boys	0.98 (0.78–1.25)	0.93 (0.72–1.20)	1.29 (1.02–1.64)†	1.25 (0.97–1.62)	1.16 (0.91–1.49)	1.09 (0.84–1.43)	1.42 (0.73–2.77)	1.25 (0.60–2.61)
Girls	1.38 (1.07–1.78)†	1.43 (1.07–1.90)†	1.27 (0.98–1.64)	1.33 (0.99–1.79)	1.33 (1.04–1.69)†	1.44 (1.09–1.89)‡	1.96 (1.06–3.64)†	2.16 (1.09–4.27)†
Adiposity (sum of skinfold ≥90th percentile)‖								
Overall	1.30 (1.06–1.60)†	1.33 (1.05–1.69)†	1.36 (1.10–1.68)‡	1.36 (1.08–1.73)†	1.23 (0.99–1.51)	1.28 (1.00–1.64)†	1.16 (0.65–2.09)	1.02 (0.52–1.98)
Boys	1.10 (0.82–1.46)	1.12 (0.80–1.56)	1.20 (0.90–1.60)	1.14 (0.82–1.57)	1.04 (0.77–1.41)	1.01 (0.71–1.45)	0.76 (0.29–1.99)	0.45 (0.13–1.57)
Girls	1.60 (1.18–2.17)‡	1.79 (1.24–2.57)‡	1.60 (1.16–2.19)‡	1.76 (1.21–2.56)‡	1.45 (1.08–1.95)†	1.55 (1.09–2.20)†	1.68 (0.78–3.61)	1.63 (0.70–3.78)
Prehypertensive or hypertensive (BP ≥90th percentile)¶								
Overall	1.11 (0.92–1.33)	1.07 (0.89–1.30)	1.25 (1.04–1.50)†	1.22 (1.01–1.48)†	1.19 (1.00–1.43)	1.17 (0.96–1.41)	1.20 (0.73–1.97)	1.15 (0.69–1.92)
Boys	1.11 (0.86–1.43)	1.06 (0.81–1.38)	1.20 (0.93–1.55)	1.16 (0.89–1.53)	1.18 (0.90–1.55)	1.16 (0.87–1.54)	0.97 (0.44–2.14)	0.99 (0.44–2.22)
Girls	1.11 (0.86–1.43)	1.08 (0.83–1.42)	1.30 (1.01–1.68)†	1.28 (0.97–1.70)	1.20 (0.94–1.53)	1.18 (0.91–1.53)	1.39 (0.73–2.67)	1.29 (0.65–2.54)

Data are OR (95% CI). ORs were for an increase of 1 SD in maternal glucose level (0.3 mmol/L for fasting PG, 1.6 mmol/L for 1-h PG, 1.3 mmol/L for 2-h PG). Corresponding ORs were then calculated for the selected sex. All ORs were adjusted for maternal age (at expected date of confinement), parity (at the index pregnancy), BMI before pregnancy, and children's exercise level, in addition to *current maternal and paternal DM status, children's age, and/or sex, as appropriate; §current maternal and paternal DM status; ‖current maternal and paternal DM status and children's age, height, and/or sex, as appropriate; or ¶current maternal hypertensive status. †P value between 0.01 and < 0.05. ‡$P < 0.01$.

overweight or obesity and of adiposity, but the association was confined to girls. The maternal 1-h PG level also was associated with increased odds of the offspring having prehypertension or hypertension.

Multivariable linear regression analysis showed children's AUC(G) at the OGTT significantly increased per 1-SD increase in maternal 1-h and 2-h PG at the OGTT, respectively, in boys (OR 19.1 [95% CI 7.5–30.6], $P = 0.001$ and 23.6 [11.4–35.8], $P < 0.001$) and girls (17.8 [5.1–30.4], $P = 0.006$ and 23.8 [11.8–35.9], $P < 0.001$) after adjusting for the same confounding factors as for abnormal glucose tolerance (listed in Table 2).

We also examined the association of abnormal glucose tolerance in offspring with different maternal and neonatal characteristics, as well as other potential risk factors at the follow-up assessment (Supplementary Table 2). None of the antenatal (advanced maternal age [≥35 years], obesity before pregnancy, gestational weight gain), neonatal (macrosomia, large for gestational age, small for gestational age), or parental characteristics (mother's diabetes status, maternal obesity) were associated with children's abnormal glucose tolerance. However, the children's adiposity (OR 3.24 [95% CI 1.14–9.21], $P = 0.03$), but not overweight or obesity, was associated with abnormal glucose tolerance at 7 years of age. We also did not find any association between being born large for gestational age and childhood overweight or obesity in this cohort.

In additional analyses including further adjustment for being born large for gestational age, adiposity at birth, overweight or obesity, or adiposity at the time of follow-up, maternal glycemic levels and maternal GDM remained significantly associated with an increased risk of abnormal glucose tolerance in the offspring (Table 3).

CONCLUSIONS

In this prospective follow-up study of mothers and offspring from the HAPO cohort, we observed a graded effect of maternal glycemic levels during pregnancy on the offsprings' risk of abnormal glucose tolerance, obesity, and adiposity at 7 years of age, after adjusting for antenatal, neonatal, and postnatal confounders. Consistent with a

Table 3—The association of offspring diagnosed with abnormal glucose tolerance with maternal glucose levels at pregnancy during OGTT and diagnosed with GDM at pregnancy

	Children's abnormal glucose tolerance after adjustment for parental and children's characteristics* and the following parameter			
	Fasting PG	1-h PG	2-h PG	GDM
Adiposity at birth†	1.90 (1.15–3.15)	2.02 (1.17–3.49)	2.25 (1.30–3.88)	4.13 (1.33–12.8)
LGA at birth‡	1.84 (1.17–2.87)	1.92 (1.15–3.19)	1.99 (1.20–3.30)	3.00 (1.01–8.87)
Adiposity at 7 years§	1.80 (1.17–2.78)	1.91 (1.16–3.14)	1.97 (1.19–3.27)	3.13 (1.05–9.30)
Overweight/obese at 7 years‖	1.85 (1.20–2.85)	1.90 (1.15–3.14)	1.96 (1.18–3.25)	2.99 (1.00–8.88)

Data are OR (95% CI). LGA, large for gestational age. *ORs adjusted for maternal age (at expected date of confinement), parity (at index pregnancy), BMI before pregnancy, current maternal and paternal DM status, children's exercise level, children's age, and sex, in addition to †sum of skinfold thickness ≥90th percentile at birth; ‡birth weight ≥90th percentile; §sum of skinfold thickness ≥90th percentile at 7 years of age; ‖BMI ≥85th percentile at 7 years of age, for an increase of 1 SD in maternal glucose level (0.3 mmol/L for fasting PG, 1.6 mmol/L for 1-h PG, 1.3 mmol/L for 2-h PG).

previous report, the graded effect of maternal hyperglycemia on obesity and adiposity in offspring was most evident among girls (33). On the other hand, Lingwood et al. (34) reported that boys were more immediately sensitive to maternal hyperglycemia in developing neonatal adiposity. In the MFMU trial, male infants born to mothers who received treatment had lower birth weight and fat mass than those born to mothers who received no treatment, but this was not apparent in female infants (35). To the contrary, at 5–10 years of age, those girls whose mothers received antenatal treatment did have lower fasting PG levels, insulin resistance, BP, and rate of IFG (3). These findings suggest that boys and girls might differ in the immediate and latent responses of adiposity and glucose metabolism to maternal hyperglycemia.

Because of the low prevalence of abnormal glucose tolerance in this young population, our relatively small sample size, and the short duration of observation, we were not able to detect sex differences in abnormal glucose tolerance. Nevertheless, we discovered a continuous association between maternal glycemic levels during pregnancy and glycemic levels of offspring, as reflected by the AUC(G) at the OGTT, to the same extent in both sexes, independent of confounders including maternal age, parity, obesity, children's exercise level, and parental DM status. We also observed a lower oral disposition index and a trend toward reduced pancreatic β-cell function among the OGDM; such may explain the mechanism underlying abnormal glucose tolerance and hyperglycemia in offspring. We also explored whether the apparent association between in utero hyperglycemia and children's glucose intolerance could be related to being born large for gestational age or having childhood obesity. First, we did not observe any associations of overweight or obesity and adiposity of children at follow-up with their weight, adiposity, or cord blood C-peptide levels at birth. Second, only childhood adiposity, and not overweight or obesity, was shown to be associated with abnormal glucose tolerance in the children. Finally, despite adjusting for offsprings' BMI and adiposity (either at birth or at the time of follow-up), all three glycemic levels during pregnancy and GDM status remained significantly associated with an increased risk of abnormal glucose tolerance in the offspring. This observation suggests that the association between maternal glucose levels and abnormal glucose tolerance in offspring is not necessarily mediated through macrosomia at birth or childhood obesity.

The association between maternal glycemia in pregnancy and prehypertension or hypertension in the children was only observed for maternal glucose at the first hour of the OGTT during pregnancy. This could be due to the low prevalence of hypertension among this young age group, rendering it underpowered to detect any association with other glycemic levels. On the other hand, the result may highlight the relevance of adding the 1-h glucose level to the revised World Health Organization diagnostic criteria.

The HAPO follow-up study from Belfast did not reveal any association between maternal hyperglycemia and childhood obesity and adiposity (17). The dissimilar findings may be because of different study designs and interethnic differences in genetic and environmental factors. Overall, the children in the Belfast study were younger, with the youngest being 5 years old. As reported in a previous prospective study, the effect of maternal diabetes on later childhood abnormalities became evident only after the age of 5 years (10). In addition, our subjects were all Chinese, and thus our study results may not be generalizable to other ethnic groups. To this end, because the Hong Kong and the Belfast cohorts had ongoing follow-up studies of children at the same ages, comparisons between the outcomes of these two populations would be of interest.

Other than the limitations mentioned above, this study has several advantages in its design. The OGTT result during the index pregnancy remained undisclosed and the mothers received no antenatal treatment or postnatal intervention for their hyperglycemia. Children were assessed at the same age, with a 96% completion rate of the five-point OGTT with insulin levels. Our cohort also had available comprehensive data from during pregnancy and at delivery, and we had children's dietary histories and exercise levels available for adjustment for various confounders.

In summary, in this follow-up study of the HAPO cohort, we observed that maternal hyperglycemia increased the risk of abnormal glucose tolerance, obesity, and hypertension among offspring in early childhood, independent of maternal obesity, being large for gestational age at birth, and childhood obesity. Despite the low frequency of abnormal glucose tolerance among children of this young age, this cardiometabolic risk might continue to increase throughout adolescence into adulthood. A multicenter

follow-up study of offspring (aged 8–12 years) of mothers recruited from 10 of the original 15 HAPO study centers is under way. While this larger-scale multiethnic study will shed light on the long-term consequences of GDM, our data emphasize the need to follow up with offspring of mothers with GDM who are at risk for reduced β-cell function and abnormal glucose tolerance, especially in Asia, where GDM, childhood obesity, young-onset DM, and premature chronic diseases are rampant (36,37).

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