Associations of gestational glycemia and prepregnancy adiposity with offspring growth and adiposity in an Asian population[1,2]

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ABSTRACT

Background: Maternal obesity and hyperglycemia increase risk of obesity and diabetes in offspring later in life.

Objective: We examined the relation between gestational glycemia and prepregnancy body mass index (ppBMI) with offspring growth in an Asian mother-offspring cohort.

Design: Pregnant mothers undertook a 75-g 2-h oral-glucose-tolerance test at 26–28 wk of gestation. In 937 singleton offspring, ≤9 serial measurements of weight and length were obtained from birth until 36 mo of age.

Results: Gestational fasting plasma glucose (FPG) was positively associated with birth weight (*B*: 0.17; 95% CI: 0.10, 0.24; $P < 0.001$) and birth BMI (*B*: 0.15; 95% CI: 0.06, 0.40; $P = 0.001$) but not at ≥3 mo of age. In contrast, maternal ppBMI was positively associated with birth variables and conditional growth in weight and BMI in the first 36 mo of life. However, gestational FPG and prepregnancy obesity status interacted significantly for the association with offspring growth and overweight status in the first 36 mo of life (*P*-interaction < 0.01). In nonobese mothers, each unit increase in gestational FPG was associated with increased offspring weight (*B*: 0.08; 95% CI: 0.008, 0.16; $P = 0.03$) and BMI (*B*: 0.08; 95% CI: 0.003, 0.15; $P = 0.04$) as well as increased risk of overweight in the first 36 mo of life (OR: 1.36; 95% CI: 1.10, 1.68). However, in obese mothers, each unit increase in gestational FPG was associated with decreased offspring weight (*B*: −0.01; 95% CI: −0.02, −0.003) and BMI (*B*: −0.008; 95% CI: −0.01, −0.002) velocity ($P < 0.01$ for both) and decreased risk of overweight (OR: 0.59; 95% CI: 0.41, 0.86) in the first 36 mo of life.

Conclusions: Prepregnancy adiposity was associated with offspring growth in early childhood. Although pooled analyses showed no demonstrable difference by 3 mo of age, there were contrasting and opposite associations of gestational glycemia with weight and BMI in the first 36 mo of life in offspring of nonobese and obese mothers separately. This study was registered at clinicaltrials.gov as NCT01174875. *Am J Clin Nutr* doi: 10.3945/ajcn.115.117614.

Keywords: gestational glycemia, offspring growth and body composition, prepregnancy obesity

INTRODUCTION

Obesity and type 2 diabetes present massive health challenges because they have rapidly become worldwide epidemics (1). Hence, an understanding of the pathogenesis is important to formulate treatment and prevention strategies. Developmental influence on obesity risk that originates from the maternal intrauterine environment has been put forth as one of the mechanisms that confer susceptibility to excessive adiposity (2). One of the earliest evidence of developmental plasticity conferring obesity susceptibility came from the Dutch famine study, which studied the offspring of women who conceived during the Dutch famine of 1944 when an embargo was placed on all food supplies to the Netherlands (3, 4). Besides maternal nutrition during pregnancy, maternal prepregnancy obesity and hyperglycemia during pregnancy have been documented to be associated with a higher birth weight of offspring (5), which carries with it an inherently greater risk of diabetes and obesity in later life (6–8). There has also been evidence that suggested that early postnatal growth patterns predict subsequent adiposity and obesity risk in childhood as described in The Quebec Longitudinal Study of

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[2] Supplemental Figures 1 and 2 and Supplemental Tables 1 and 2 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Child Development in Canada (9) and, more recently, in the Fels Longitudinal Study (10).

When studying pregnant women, a true BMI estimation can be problematic because body weight increases with advancing gestation. The Royal College of Obstetricians and Gynecologists and the Centre for Maternal and Child Inquiries in the United Kingdom (11) have suggested classifying a pregnant woman as obese once BMI (in kg/m^2) that is measured at the initial booking is ≥30, whereas the Society of Obstetricians and Gynaecologists of Canada suggested that pregnant women can be considered obese once prepregnancy BMI (ppBMI)[13] is ≥30 (12). At present, it is unclear whether there is a specific BMI criterion for pregnant Asian women. In addition, it is believed that excessive exposure to increased glucose from the mother during pregnancy may contribute to an excessive weight gain of the offspring born to diabetic mothers (13). The influence of gestational glycemia on early postnatal growth has been described (14, 15) but can still be better defined, especially for associations with the offspring growth pattern across the range of glucose concentrations, even for women who are below the diagnostic cutoff for gestational diabetes mellitus (GDM). In addition, because of the paucity of existing data on prenatal metabolic exposures and infant growth in Asian populations and because the Asian phenotype and susceptibility toward obesity and metabolic disease differs from that of Europeans (16), additional studies on the relation between gestational glycemia with offspring growth in Asian populations is merited. Thus, we sought to examine the associations of gestational glycemia and ppBMI in relation to birth measures and the postnatal growth of offspring during the first 36 mo of life with the use of data from the GUSTO (Growing Up in Singapore Towards healthy Outcomes) study (clinicaltrials.gov; NCT01174875), which is an Asian mother-offspring cohort study in Singapore.

METHODS

Study population

The GUSTO study has been previously described in detail (17). Briefly, pregnant women in their first trimester were recruited from 2 major public hospitals with obstetric services in Singapore (i.e., the KK Women's and Children's Hospital and the National University Hospital) between June 2009 and September 2010. Women approached were Singapore citizens or permanent residents who were of Chinese, Malay, or Indian ethnicity with homogeneous parental ethnic backgrounds. Women who were receiving chemotherapy, taking psychotropic drugs, or had diabetes mellitus were excluded. Of 3751 screened women, 2034 individuals met these criteria, and 1247 women (response rate: 61.3%) were recruited of whom 1152 women had singleton naturally conceived pregnancies and deliveries (**Supplemental Figure 1**). This study was approved by both the National Healthcare Group Domain Specific Review Board and the SingHealth Centralized Institutional Review Board.

[13] Abbreviations used: FPG, fasting plasma glucose; GA, gestational age; GDM, gestational diabetes mellitus; GUSTO, Growing Up in Singapore Towards healthy Outcomes; LME, linear mixed effects; ppBMI, prepregnancy BMI; SDS, SD score; 2h-PG, 2-h postchallenge glucose.

Assessment of gestational age

Gestational age (GA) was assessed with the use of ultrasonography. In all women, GA was first assessed in the first ultrasound dating scan during recruitment in the first trimester. Scans were conducted in a standard manner at both hospitals by trained ultrasonographers. GA was reported in completed weeks.

Oral-glucose-tolerance testing

Pregnant women underwent a 2-h 75-g oral-glucose-tolerance test after an overnight fast at 26–28 wk of gestation, and venous plasma glucose was measured with the use of colorimetry [Advia 2400 Chemistry system (Siemens Medical Solutions Diagnostics) and Beckman LX20 Pro analyzer (Beckman Coulter)]. During the study period, glucose management was performed when mothers were diagnosed with hyperglycemia according to WHO criteria (fasting or 2-h plasma glucose concentrations >7.0 or >7.8 mmol/L, respectively). Results were communicated to health practitioners, and mothers who were positively diagnosed were placed under a diet or insulin treatment of management. Mothers with elevated fasting or 2-h plasma glucose were subjected to the same glucose-management protocol. Questionnaires were administered during the visit to ascertain demographics and socioeconomic status.

Anthropometric measures

Maternal prepregnancy weight was self-reported at study enrollment. At 26–28 wk of gestation, maternal weight and height were measured with the use of a SECA 803 Weighing Scale (SECA Corp.) and a SECA 213 Stadiometer (SECA Corp.), respectively. Maternal ppBMI was calculated as self-reported prepregnancy weight divided by the square of height. Prepregnancy obesity was defined as ppBMI ≥30. Four-site skinfold thickness measurements (triceps, biceps, subscapular, and suprailliac) were measured in triplicates with the use of Holtain skinfold thickness calipers (Holtain Ltd.) on the right side of the body and recorded to the nearest 0.2 mm.

Anthropometric measurements of offspring weight and length were obtained at birth and at 3, 6, 9, 12, 15, 18, 24, and 36 mo of age. Infant weight from birth until 18 mo of age was measured to the nearest gram with the use of a calibrated scale (SECA 334 Weighing Scale; SECA Corp.). At 24 and 36 mo of age, weight was measured to the nearest gram with the use of a SECA 803 Weighing Scale. Recumbent infant length from birth to 24 mo of age was measured from the top of the head to the soles of the feet with the use of an infant mat (SECA 210 Mobile Measuring Mat; SECA Corp.) to the nearest 0.1 cm. Standing height at 36 mo of age was measured with the use of the SECA 213 Stadiometer from the top of the participant's head to his or her heels to the nearest 0.1 cm. For reliability, all measurements were taken in duplicates and averaged.

Infant feeding

Mothers were asked about infant milk feeding with the use of questionnaires that were bases on a 24-h recall at routine house visits when infants were 3, 6, 9, and 12 mo of age. In accordance with WHO guidelines (18), feeding practices were classified into exclusive, predominant, partial breastfeeding, and formula

feeding. In our data collection, both direct breastfeeding and expressed breast-milk intakes were classified as breastfeeding.

Statistical analysis

Descriptive statistics were reported as means ± SDs for continuous variables and percentages for categorical variables. Fasting plasma glucose (FPG) and 2-h postchallenge glucose (2h-PG) measurements were assessed as both continuous and categorical variables divided into quartiles. For FPG, quartiles were as follows: first, <4.1 mmol/L); second, 4.1 to <4.3 mmol/L); third, 4.3 to <4.6 mmol/L); and fourth, ≥4.6 mmol/L. For 2h-PG, quartiles were as follows: first, <5.5 mmol/L; second, 5.5 to <6.3 mmol/L); third (6.3 to <7.3 mmol/L); and forth, ≥7.3 mmol/L. Age- and sex-specific SD scores (SDSs) were calculated for weight, length, and BMI at all time points with reference to the local Singapore population (19) (Ministry of Health Singapore, personal communication, 2015). Offspring overweight status was defined as having BMI greater than the 85th percentile (i.e., BMI SDS >1.036). The SDS was also produced for maternal FPG, 2h-PG, and ppBMI.

Offspring conditional growth was derived from standardized residuals resulting from the regression of the SDS for a measurement at a specific time point on the SDS for measurements at preceding ages (20). For example, the dependent variable of conditional growth in weight SDS from 0–3 mo of age was derived as the residual of the regression of weight SDS at 3 mo of age on the weight SDS at birth. Multivariable linear regression analyses were used to estimate associations between maternal glucose concentrations and ppBMI with offspring conditional growth, in all cases with adjustment for ethnicity, parity, maternal age, education, height at 26–28 wk of gestation, gestational weight gain until 26–28 wk of gestation, and breastfeeding duration. In view of mothers who received treatment for hyperglycemia, we further corrected for potential confounding by glucose management (diet and insulin treatment) in the regression models. Potential effect modifications by prepregnancy obesity status were investigated by adding the interaction term of glucose with prepregnancy obesity status to the fully adjusted model. Because the associations were assessed at 9 time points for each outcome of conditional growth in weight, length, and BMI, a more stringent cutoff of $P < 0.005$ was considered statistically significant, and $P < 0.01$ was considered as trend associations for each outcome.

In addition, we examined the longitudinal effect of glucose concentrations on weight and BMI SDS growth trajectory with the use of linear mixed effects (LME) models, which took into account the correlation between repeated measures on the same individual and allowed for incomplete outcome data with the assumption that it was missing at random (21). Maximum likelihood was the method of estimation used, and an unstructured working covariance matrix for random effects variables (intercept and slope) was chosen. The Akaike information criterion statistic facilitated the model selection, and final models included linear, quadratic, and cubic terms for children's ages and age-glucose interactions to estimate the change in weight and BMI SDS over time associated with a unit SDS increase in glucose concentrations. Besides the fixed effect of age, we allowed for a random intercept and random linear slope for age. We also tested the associations of gestational glycemia with child overweight with the use of generalized estimating equations to model the odds of being overweight in the first 36 mo of life longitudinally with adjustment for ethnicity, parity, maternal age, education, height at 26–28 wk of gestation, gestational weight gain until 26–28 wk of gestation, and breastfeeding duration. Similar to LME models, generalized estimating equation models are often used for repeated-measures data because they accounts for the within-subject correlation between observations across time and can allow for missing data in the outcome measure. Because growth velocities in offspring of obese and nonobese women are different (22), separate models were constructed. All analyses were performed with the use of Stata 13 software (StataCorp LP).

RESULTS

Complete data on glucose concentrations and ppBMI were available for 937 women (Supplemental Figure 1). There were no significant differences in sociodemographic characteristics (education, ethnicity, marital status, and housing type) between women included ($n = 937$) and excluded ($n = 300$) in the study sample except for parity ($P = 0.005$) (**Supplemental Table 1**). Characteristics of mothers included in the study sample are shown in **Table 1**. Most of the mothers' characteristics differed significantly across ethnic groups, including maternal age ($P < 0.001$), education ($P < 0.001$), housing type ($P < 0.001$), parity ($P = 0.015$), ppBMI ($P < 0.001$), prepregnancy obesity status ($P < 0.001$), gestational weight gain ($P = 0.029$), breastfeeding duration ($P < 0.001$), FPG ($P = 0.001$), and 2h-PG concentrations ($P = 0.001$) and GDM treatment type ($P = 0.004$). Indian mothers reported highest glucose concentrations ($P < 0.001$), whereas Malay mothers reported highest ppBMI ($P < 0.001$), proportion of obesity ($P < 0.001$), and gestational weight gain ($P = 0.042$). Chinese and Indian mothers were of higher socioeconomic status (education and type of housing) than Malay mothers were ($P < 0.001$ for all). Offspring characteristics also differed significantly across ethnic groups, including birth length and BMI ($P = 0.024$ and $P = 0.001$, respectively).

Figure 1A–C highlights the association of gestational FPG SDS with offspring conditional growth in the first 36 mo of life. The FPG SDS had significant positive associations with birth-weight SDSs (B: 0.17; 95% CI: 0.10, 0.24; $P < 0.001$) and birth-BMI SDSs (0.15; 95% CI: 0.06, 0.40; $P = 0.001$), but no significant associations with the serial anthropometric measures were observed from ≥3 mo of age after adjustment for potential confounders. 2h-PG SDSs showed positive associations with birth-weight SDSs only (0.07; 95% CI: 0.01, 0.15; $P = 0.03$) (data not shown). In contrast, maternal ppBMI SDSs showed a significant association with birth-weight SDSs (0.21; 95% CI: 0.14, 0.28; $P < 0.001$), conditional growth in weight SDSs between 0–36 mo of age (0.09; 95% CI: 0.007, 0.17; $P = 0.033$) (**Figure 2**A), and birth-length SDSs (0.09; 95% CI: 0.03, 0.17; $P = 0.007$) (Figure 2B). Maternal ppBMI SDSs also showed positive associations with birth-BMI SDSs (0.11; 95% CI: 0.02, 0.20; $P = 0.021$) and conditional growth in BMI SDSs between 0–12 mo of age (0.10; 95% CI: 0.02, 0.19; $P = 0.018$), 0–18 mo of age (0.11; 95% CI: 0.01, 0.20; $P = 0.024$), 0–24 mo of age (0.14; 95% CI: 0.05, 0.23; $P = 0.002$), and 0–36 mo of age (0.19; 95% CI: 0.10, 0.27; $P < 0.001$) (Figure 2C).

TABLE 1
Demographic and clinical characteristics of study subjects

	Chinese	Malay	Indian	Total	P^1
Mothers, *n*	516	252	169	937	
Age, y	31.5 ± 4.9[2]	28.9 ± 5.5[3]	29.8 ± 4.7[3]	30.5 ± 5.2	<0.001
Marital status, *n* (%)					0.352
Married	495 (96.3)	241 (95.6)	166 (98.2)	902 (96.5)	
Single	19 (3.7)	11 (4.4)	3 (1.8)	35 (3.5)	
Years of education, *n* (%)					<0.001
<12	155 (30.0)	174 (69.0)	52 (30.8)	381 (40.7)	
≥12	361 (70.0)	78 (31.0)[3]	117 (69.2)	556 (59.3)	
Type of housing, *n* (%)					<0.001
Government	457 (88.6)	250 (99.2)	154 (91.1)	861 (91.9)	
Private	59 (11.4)	2 (0.8)[3]	15 (8.9)	76 (8.1)	
Breastfeeding duration, *n* (%)					<0.001
Formula only	71 (14.8)	49 (21.6)	23 (14.9)	143 (16.6)	
<4 mo	279 (58.0)	156 (68.7)	97 (63.0)	532 (61.7)	
≥4 mo	131 (27.2)	22 (9.7)[3]	34 (22.1)	187 (21.7)	
Parity, *n* (%)					0.015
Primiparous	243 (47.8)	101 (40.9)	60 (35.9)	404 (43.8)	
Multiparous	265 (52.2)	146 (59.1)	107 (64.1)[3]	518 (56.2)	
Prepregnancy obesity, *n* (%)					<0.001
Nonobese (<30 kg/m^2)	502 (97.3)	215 (85.3)	154 (91.1)	871 (93.0)	
Obese (≥30 kg/m^2)	14 (2.7)	37 (14.7)[3]	15 (8.9)[3]	66 (7.0)	
Prepregnancy BMI, kg/m^2	21.5 ± 3.3	24.2 ± 5.5[3]	23.8 ± 4.4[3]	22.7 ± 4.4	<0.001
Gestational weight gain until 26–28 wk, kg	8.5 ± 3.7	9.2 ± 5.8[3]	8.0 ± 4.5	8.6 ± 4.5	0.029
Plasma glucose, mmol/L					
Fasting	4.3 ± 0.4	4.3 ± 0.5	4.5 ± 0.5[3]	4.3 ± 0.5	0.001
2 h	6.6 ± 1.4	6.2 ± 1.5[3]	6.6 ± 1.6	6.5 ± 1.5	0.001
GDM treatment type, *n* (%)					0.004
No	409 (80.0)	222 (90.2)	130 (77.8)	761 (82.4)	
Diet treatment	95 (18.6)	21 (8.5)[3]	34 (20.4)	150 (16.2)	
Insulin treatment	7 (1.4)	3 (1.2)	3 (1.8)	13 (1.4)	
Offspring					
Gestational age at delivery, wk	38.3 ± 1.5	38.2 ± 1.3	38.2 ± 1.5	38.3 ± 1.5	0.182
Sex, *n* (%)					0.684
M	248 (48.4)	112 (45.2)	81 (48.2)	441 (47.5)	
F	264 (51.6)	136 (54.8)	87 (51.8)	487 (52.5)	
Birth weight, kg	3.1 ± 0.5	3.1 ± 0.4	3.0 ± 0.5	3.1 ± 0.5	0.145
Birth length, cm	48.8 ± 2.3	48.3 ± 2.0[3]	48.6 ± 2.2	48.6 ± 2.3	0.024
Birth BMI, kg/m^2	13.0 ± 1.3	13.3 ± 1.3[3]	12.8 ± 1.4	13.0 ± 1.3	0.001

[1] *P* values across 3 ethnic groups were determined with the use of a chi-square analysis (categorical) or 1-factor ANOVA (continuous). GDM, gestational diabetes mellitus.

[2] Mean ± SD (all such values).

[3] $P < 0.05$ compared with Chinese [determined with the use of a chi-square analysis (categorical) or 2-sample *t* test (continuous)].

We noted that gestational FPG and prepregnancy obesity status interacted significantly for the association with offspring conditional growth in weight SDSs between 0–18 mo of age ($P = 0.025$), 0–24 mo of age ($P = 0.012$) and 0–36 mo of age ($P = 0.003$) as well as for the outcome of conditional growth in BMI SDSs between 0–18 mo of age ($P = 0.011$), 0–24 mo of age ($P = 0.013$), and 0–36 mo of age ($P = 0.015$) (**Supplemental Table 2**), which implied that the relation between gestational FPG with offspring growth in the first 36 mo of life appears to be modified by prepregnancy obesity status. In a fully adjusted LME model for nonobese women (**Figure 3**A, C), we observed that, on average, the FPG SDS was positively associated with offspring weight and BMI SDSs across the first 36 mo of life ($P = 0.03$ and $P = 0.04$, respectively) with every unit increase in the FPG SDS increasing the weight SDS by 0.08 units (95% CI: 0.008, 0.16 units) and BMI SDS by 0.08 units (95% CI: 0.003, 0.15 units). In addition, gestational FPG and prepregnancy obesity status interacted significantly for the association with offspring overweight in the first 36 mo of life ($P < 0.001$). In nonobese mothers, a higher FPG SDS was associated with increased risk of being overweight in the first 36 mo of life ($P = 0.001$) with each unit increase in the FPG SDS increasing the odds of offspring overweight by 36% (OR: 1.36; 95% CI: 1.10, 1.68) after adjustment for potential confounders (**Table 2**). This observation might have been due to the increasing severity in maternal adiposity at 26–28 wk of gestation across increasing FPG in nonobese mothers (**Table 3**); nevertheless, the results were still significant when adjusted for maternal adiposity (sum of skinfold-thicknesses) at 26–28 wk of gestation (Table 2).

However, in a fully adjusted LME model for obese women (Figure 3B, D), we noted a decrease in weight and BMI SDS velocity across age with an increasing FPG SDS ($P = 0.003$ and $P = 0.009$, respectively) with an estimated rate of decrease of

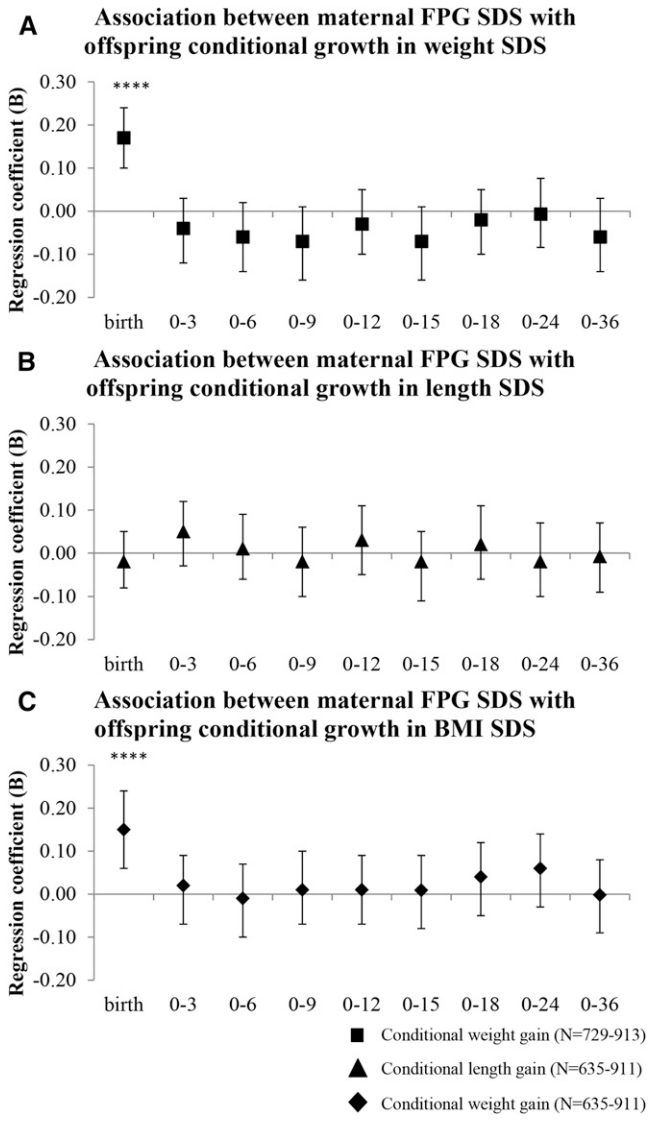

FIGURE 1 Associations (regression coefficients ± 95% CIs) between maternal FPG SDSs at 26–28 wk of gestation with offspring conditional growth in weight SDSs (A), length SDSs (B), and BMI SDSs (C) in the first 36 mo of life. All models were analyzed with the use of multivariable linear regression with adjustment for ethnicity, parity, maternal age, maternal education, prepregnancy BMI, gestational weight gain until 26–28 wk of age, gestational diabetes mellitus treatment type, and breastfeeding duration. ****$P < 0.001$. FPG, fasting plasma glucose; SDS, SD score.

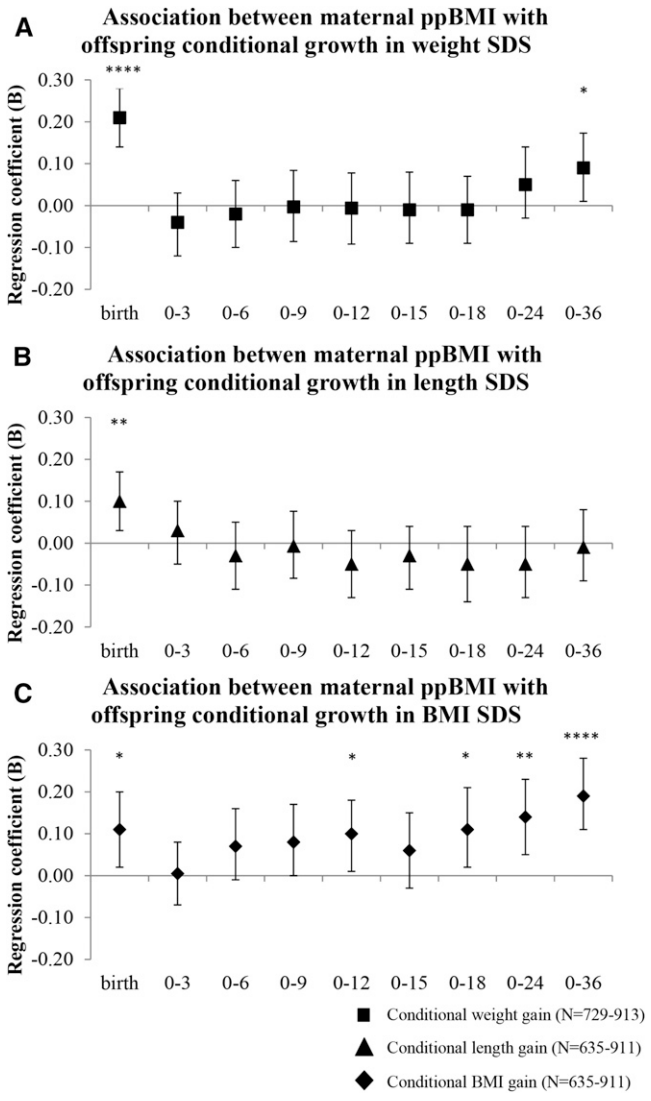

FIGURE 2 Associations (regression coefficients ± 95% CIs) between maternal ppBMI SDSs with offspring conditional growth in in weight SDSs (A), length SDSs (B), and BMI SDSs (C) in the first 36 mo of life. All models were analyzed with the use of multivariable linear regression with adjustment for ethnicity, parity, maternal age, maternal education, prepregnancy BMI, gestational weight gain until 26–28 wk, gestational diabetes mellitus treatment type, and breastfeeding duration. Data are shown as regression coefficient ± 95% confidence intervals. *$P < 0.05$, **$P < 0.01$, ****$P < 0.001$. ppBMI, prepregnancy BMI; SDS, SD score.

0.01 weight SDS units/mo (95% CI: −0.02, −0.003 weight SDS units/mo) and 0.008 BMI SDS units/mo (95% CI: −0.01, −0.002 BMI SDS units/mo) for every unit SDS increase in FPG. Furthermore, an increasing FPG SDS was associated with decreased risk of being overweight in the first 36 mo of life with each unit increase in the FPG SDS decreasing the odds of offspring overweight by 41% (OR: 0.59; 95% CI: 0.41, 0.86) (Table 2). This reverse pattern might have been due to differences in adiposity severity at 26–28 wk of gestation, the ethnic distribution, and the breastfeeding duration across FPG quartiles, but we did not find any significant differences of these factors (Table 3).

We conducted additional sensitivity analyses by restricting the analyses to mothers without GDM (n = 763). In a fully adjusted LME model for nonobese, non-GDM women (n = 717), we observed that, on average, the FPG SDS was positively associated with offspring weight and the BMI SDS across the first 36 mo of life (P = 0.029 and P = 0.017, respectively),with every unit increase in the FPG SDS increasing the weight SDS by 0.10 units (95% CI: 0.01, 0.20 units) and the BMI SDS by 0.11 units (95% CI: 0.02, 0.20 units) (**Supplemental Figure2**A, C). However, in a fully adjusted LME model for obese, non-GDM women (n = 46), we noted a decrease in BMI SDS velocity across age with an increasing FPG SDS (P = 0.044) with an estimated rate of decrease of 0.009 BMI SDS units/mo (95% CI: −0.02, −0.002 BMI SDS units/mo) for every unit SDS increase in FPG (**Supplemental Figure 2**D).

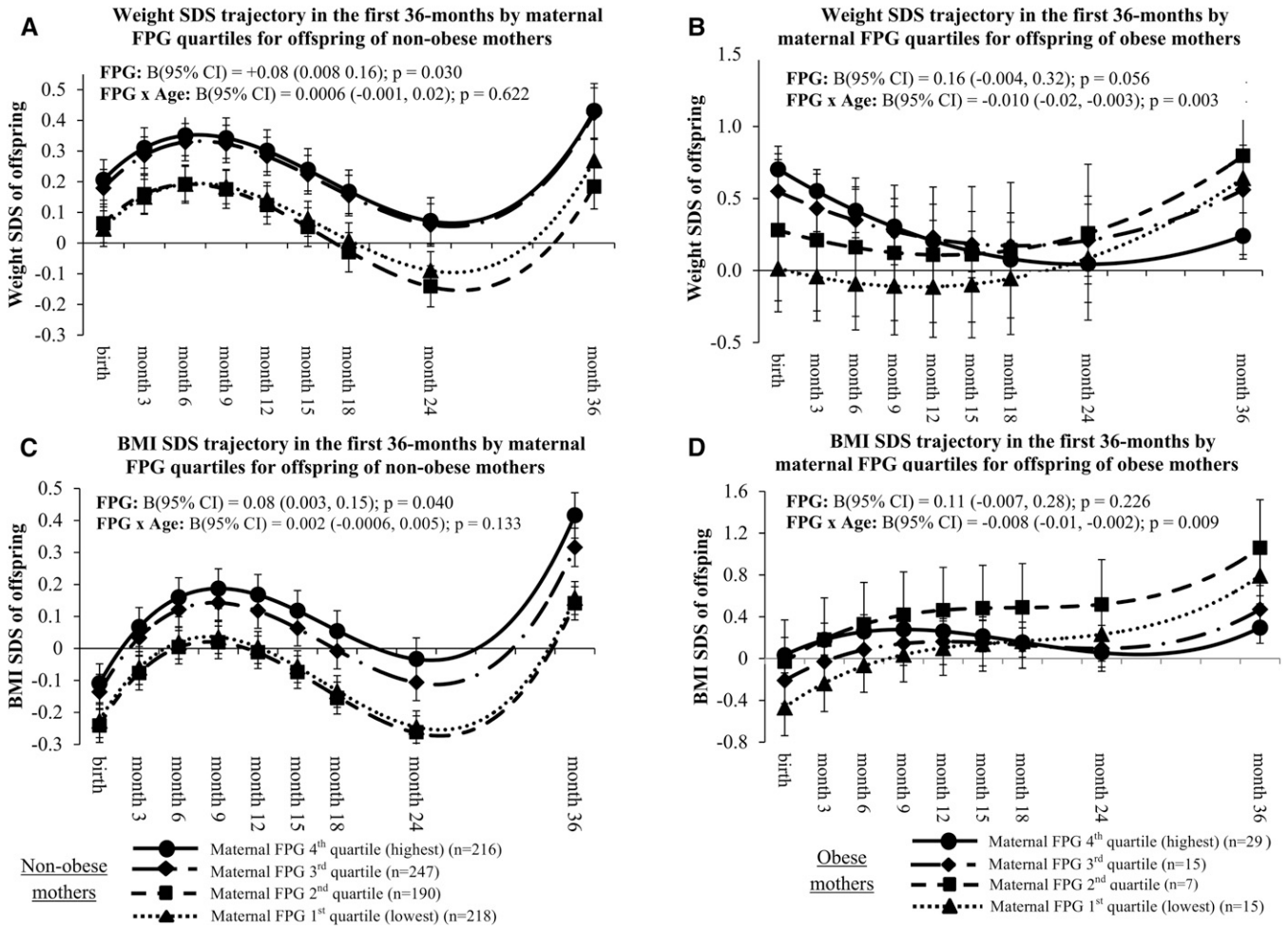

FIGURE 3 Offspring weight and BMI SDS trajectory in the first 36 mo of life shown according to categories of fasting glucose measured at 26–28 wk of gestation in offspring of nonobese women (A and C) and obese women (B and D). All the models were analyzed with the use of linear mixed-effects regression with adjustment for ethnicity, parity, maternal age, maternal education, prepregnancy BMI, gestational weight gain until 26–28 wk, gestational diabetes mellitus treatment type, and breastfeeding duration. FPG categories were as follows: first quartile, <4.1 mmol/L; second quartile, 4.1 to <4.3 mmol/L; third quartile, 4.3 to <4.6 mmol/L, and fourth quartile, ≥4.6 mmol/L. FPG, fasting plasma glucose; SDS, SD score.

DISCUSSION

In summary, this study highlights the associations between gestational glycemia and prepregnancy adiposity with offspring growth in an Asian population. Consistent with earlier studies (23, 24), we showed that gestational FPG was significantly associated with anthropometric variables at birth and was most pronounced in mothers with higher FPG, whereas 2h-PG had minimal associations with growth except at birth. In addition, we showed that, in all mothers, the association of gestational glycemia on offspring growth had no demonstrable difference by 3 mo of age in contrast with ppBMI, which was associated with offspring weight and BMI in first 36 mo of life. Note that the associations for gestational FPG and ppBMI were assessed across 9 time points for each outcome of conditional growth in weight, length, and BMI and, therefore, increased the possibility of chance findings. However, our results satisfied stringent cutoffs of significance, suggesting that the observations were unlikely due to chance.

These findings are in line with those of previous studies (25) that have documented the disappearance of the association between maternal glycemia with offspring growth by 3 mo of age but a persistent association between maternal BMI with offspring weight and BMI, but not length, in the first 2 y of life. Earlier findings (26, 27) have also documented the age-associated disappearance of the association between maternal glycemia and higher child weight status at early childhood ages, and its reemergence at only school-going age, which suggested that maternal FPG in relation to subsequent higher offspring adiposity might start beyond 3 y of age. The positive relation between maternal BMI on offspring size and adiposity has been a well-observed phenomenon (28, 29), and there may be different pathways that underlie the associations between maternal BMI and postnatal growth. First, shared familial characteristics, such as socioeconomic status, may have influenced our results. Although we controlled for the in utero and present environment of offspring by taking maternal sociodemographic characteristics into account, we could not rule out the possibility of residual confounding. Breastfeeding could also be an important factor that contributes to the association of ppBMI and offspring growth. Higher maternal BMI is generally associated with shorter durations of breastfeeding (30), and breastfed children tend to grow more slowly than do formula-fed peers (31, 32).

TABLE 2
Estimated odds of child overweight in the first 36 mo of life by longitudinal logistic regression with the use of a GEE model according to maternal FPG SDSs and other covariates[1]

	Nonobese mothers (n = 871)		Obese mothers (n = 66)		
	OR (95% CI)	P	OR (95% CI)	P	P-interaction
FPG SDS × prepregnancy obesity	—	—	—	—	0.00006
FPG SDS per unit SD increase	1.36 (1.10, 1.68)	0.005	0.59 (0.41, 0.86)	0.005	—
Maternal age per year increase	1.04 (1.00, 1.08)	0.050	1.08 (0.93, 1.26)	0.324	—
≥12 y vs. <12 y of education	0.76 (0.50, 1.16)	0.204	0.25 (0.07, 0.90)	0.034	—
Malay vs. Chinese	2.81 (1.77, 4.46)	<0.001	0.49 (0.13, 1.82)	0.288	—
Indian vs. Chinese	1.80 (1.06, 3.03)	0.028	0.43 (0.04, 4.55)	0.483	—
GDM diet treatment vs. non-GDM	0.59 (0.32, 1.10)	0.094	0.62 (0.15, 2.58)	0.513	—
GDM insulin treatment vs. non-GDM	1.17 (0.29, 4.81)	0.828	—[2]	—	—
Multiparity vs. primiparity	0.70 (0.46, 1.08)	0.108	0.53 (0.11, 2.46)	0.415	—
Gestational weight gain per kilogram increase	1.05 (1.01, 1.10)	0.010	1.11 (0.99, 1.23)	0.059	—
Maternal sum of skinfold thicknesses per millimeter increase	1.01 (0.99, 1.02)	0.269	0.98 (0.94, 1.02)	0.354	—
Breastfeeding duration per month increase	1.00 (0.97, 1.04)	0.935	1.02 (0.94, 1.12)	0.631	—
Child age per year increase	1.04 (0.90, 1.21)	0.597	1.48 (0.86, 2.56)	0.158	—

[1]ORs represents the odds of being overweight in the first 36 mo of life. FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; GEE, generalized estimating equation; SDS, SD score.
[2]OR could not be calculated because there were no obese subjects who were receiving GDM insulin treatment.

Therefore, children from obese mothers could grow faster because of reduced breastfeeding. In the current study, adjustment for breastfeeding duration did not change the significant associations between ppBMI with offspring growth. Thus, our results are suggestive that ppBMI has a greater influence on childhood growth and adiposity and provide support for maternal adiposity as a strong correlate of childhood growth compared with gestational glycemia in Asian mothers and offspring.

Our findings highlighted that gestational FPG and prepregnancy obesity status interacted significantly for the association with offspring conditional growth and overweight status in the first 36 mo of life, which implies that the relation between gestational FPG with offspring growth and adiposity appears to be modified by prepregnancy obesity status. Although pooled analyses showed no demonstrable differences by 3 mo of age, we showed contrasting and opposite associations between gestational glycemia with growth and adiposity in offspring of

TABLE 3
Differences in maternal adiposity (skinfold thickness) severity at 26–28 wk of gestation, breastfeeding duration, and ethnic distribution across FPG quartiles stratified by prepregnancy obesity status[1]

	Nonobese mothers, FPG quartiles (n = 871)					Obese mothers, FPG quartiles (n = 66)					
	First (n = 218)	Second (n = 190)	Third (n = 247)	Fourth (n = 216)	P^2	First (n = 15)	Second (n = 7)	Third (n = 15)	Fourth (n = 29)	P^2	P-interaction
Triceps skinfold thickness, mm	19.9 ± 5.4[3]	21.0 ± 5.3	21.9 ± 5.6	23.8 (5.3)	<0.001	27.2 ± 5.2	31.7 ± 3.8	29.4 ± 3.7	30.2 ± 5.4	0.151	0.353
Biceps skinfold thickness, mm	10.1 ± 4.2	10.6 ± 4.3	11.9 ± 4.9	12.6 ± 4.9	<0.001	18.3 ± 6.5	18.7 ± 4.4	18.9 ± 3.9	19.9 ± 5.0	0.784	0.892
Subscapular skinfold thickness, mm	19.8 ± 6.3	20.5 ± 6.0	21.3 ± 5.9	23.1 ± 5.6	<0.001	28.1 ± 6.5	31.2 ± 5.2	29.5 ± 3.5	31.0 ± 4.2	0.261	0.750
Suprailliac skinfold thickness, mm	22.9 ± 5.7	22.6 ± 5.6	23.2 ± 5.1	25.0 ± 5.3	<0.001	28.4 ± 5.7	28.6 ± 0.4	29.0 ± 4.6	29.4 ± 4.2	0.920	0.891
Breastfeeding duration, n (%)					0.386					0.724	0.362
Formula only	36 (27.9)	18 (14.0)	39 (30.2)	36 (27.9)		3 (21.4)	3 (21.4)	2 (14.3)	6 (42.9)		
<4 mo	107 (25.7)	91 (21.8)	114 (27.3)	105 (25.2)		9 (27.3)	3 (9.1)	8 (24.2)	13 (39.4)		
>4 mo	64 (24.7)	65 (25.1)	68 (26.3)	62 (23.9)		3 (27.3)	0 (0)	(27.3)	5 (45.5)		
Ethnicity, n (%)					0.079					0.333	0.485
Chinese	124 (24.7)	118 (23.5)	148 (29.5)	112 (22.3)		2 (14.3)	1 (7.1)	4 (28.6)	7 (50.0)		
Malay	62 (28.8)	45 (20.9)	56 (26.0)	52 (24.2)		11 (29.7)	6 (16.2)	7 (18.9)	13 (35.1)		
Indian	32 (20.8)	27 (17.5)	43 (27.9)	52 (33.8)		2 (13.3)	0 (0.0)	4 (26.7)	9 (60.0)		

[1]FPG categories were as follows: first quartile, <4.1 mmol/L; second quartile, 4.1 to <4.3 mmol/L; third quartile, 4.3 to <4.6 mmol/L, and fourth quartile, ≥4.6 mmol/L. FPG, fasting plasma glucose.
[2]P values across FPG quartiles were determined with the use of a chi-square analysis (categorical) or 1-factor ANOVA (continuous).
[3]Mean ± SD (all such values).

nonobese and obese mothers when analyzed separately. Although raised FPG was associated with increased weight, BMI, and risk of overweight in offspring of nonobese women in our cohort, we observed that an increasing FPG was associated with a decreasing weight and BMI velocity over time as well as decreasing risk of overweight in offspring of obese women (Figure 3A–D), and similar observations were noted when analyses were restricted to non-GDM mothers only (Supplemental Figure 2A–D). These opposing associations could have been ameliorated when all mothers were included, thereby explaining our observations in the pooled analyses.

Our observations in nonobese mothers might have been due to the increasing severity in maternal adiposity at 26–28 wk of gestation across FPG quartiles in the study sample. However, our analyses were adjusted for maternal skinfold thickness, which indicated that the observed association was independent of maternal adiposity. Nonetheless, our results were consistent with findings by Ehrlich et al. (33). It is plausible that the effects of FPG during pregnancy would be easier to detect in offspring of nonobese women (22). The exposure to increased maternal glycemia has been associated with increased fetal hyperinsulinemia (34) and neonatal adiposity (5). The third trimester of pregnancy is also a sensitive period for adipose cell hyperplasia in mothers (35); thus, increased maternal glucose may further result in fetal exposure to increased lipid substrates during this critical period (36).

However, our observations in obese mothers were not explained by differences in adiposity severity at 26–28 wk of gestation. When a relation between raised gestational FPG with offspring growth was considered, is it necessary to consider potential differences in postnatal behaviors such as breastfeeding. Nevertheless, we observed no differences in breastfeeding duration or ethnic distribution across FPG quartiles in obese mothers in our study sample. Ehrlich et al. (33) similarly showed that there was a negative association between increasing pregnancy glucose and the offspring BMI z score in the first 3.5 y of life, and the association between increasing pregnancy glucose with an increased BMI z score in obese mothers attained near significance only at 7 y of age. Although the mechanism for these effects is still unknown, the result again suggests that, in obese mothers, the relation between maternal FPG with subsequent higher offspring adiposity might start only beyond 3 y of age.

The prospective design of our cohort was a clear strength in our study because it was crucial for the examination of the effect of in utero exposure on the outcome of offspring growth and adiposity. To date, there are a paucity of existing data on prenatal metabolic exposures and infant growth in Asian populations; thus, our study provides useful, informative data on this relation. However, there were limitations to consider. First, glucose data were collected only at fasting and 2 h postchallenge but not at 1 h postchallenge. Data on 1-h glucose would have allowed us to better address the role of gestational glycemia with offspring growth. Second, maternal prepregnancy weight was self-reported during study enrollment, which may have subjected the data to a potential recall bias. However, our data showed a strong correlation between recalled prepregnancy weight and measured weight at 26–28 wk of gestation (r = 0.923), which indicated the high reliability of the use of prepregnancy weight and BMI measures in this study. Third, the relatively small sample size of this study may have resulted in reduced power to detect interactions and certain associations, especially in analyses restricted to obese women. However, the analyses were conducted with the use of longitudinal models that made use of repeated measurements for each individual over a period of time, which would subsequently have resulted in increased power. Last, our study also lacked measures of plasma insulin, insulin growth factors, ghrelin, leptin, and adiponectin, which would have been useful to mechanistically explain the observed associations between gestational FPG and prepregnancy adiposity with offspring weight and BMI.

In conclusion, we show that prepregnancy adiposity is associated with offspring growth in early childhood. In addition, although pooled analyses showed no demonstrable difference by 3 mo of age, there are contrasting and opposite associations of gestational glycemia with weight and BMI in the first 36 mo of life in offspring of nonobese and obese mothers separately. Currently, children in the GUSTO will be followed up until 9 y of age. Future follow-up studies on these children would be essential to evaluate if our observations have long-term repercussions in later childhood.

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