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Research: Epidemiology Fetal overnutrition and offspring insulin resistance and β-cell function: the Exploring Perinatal Outcomes among Children (EPOCH) study

K. A. Sauder[1], **C. W. Hockett**[2], **B. M. Ringham**[3], **D.H. Glueck**[3], and **D. Dabelea**[1,2]

[1]Department of Pediatrics, University of Colorado School of Medicine, Colorado School of Public Health, Aurora, CO, USA

[2]Department of Epidemiology, Colorado School of Public Health, Aurora, CO, USA

[3]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO, USA

Abstract

Aims—To examine the associations of intrauterine exposure to maternal diabetes and obesity with offspring insulin resistance, β-cell function and oral disposition index in a longitudinal observational study of ethnically diverse offspring.

Methods—A total of 445 offspring who were exposed (*n*=81) or not exposed (*n*=364) to maternal diabetes *in utero* completed two fasting blood measurements at mean (sd) ages of 10.5 (1.5) and 16.5 (1.2) years, respectively, and an oral glucose tolerance test at the second visit. We used linear mixed models and general linear univariate models to evaluate the associations of maternal diabetes and pre-pregnancy BMI with offspring outcomes.

Results—Maternal diabetes *in utero* predicted increased insulin resistance [18% higher updated homeostatic model assessment of insulin resistance (HOMA2-IR), *P*=0.01; 19% lower Matsuda index, *P*=0.01 and 9% greater updated homeostatic model assessment of β-cell function (HOMA2-β), *P*=0.04]. Each 5-kg/m^2 increase in pre-pregnancy BMI predicted increased insulin resistance (11% greater HOMA2-IR, *P*<0.001; 10% lower Matsuda index, *P*<0.001; 6% greater HOMA2-β, *P*<0.001). Similar results were obtained in a combined model with both exposures. After adjustment for offspring BMI, only maternal diabetes was associated with higher HOMA2-IR (β=1.12, *P*=0.03) and lower Matsuda index (β=0.83, *P*=0.01). Neither exposure was associated with early insulin response or oral disposition index.

Conclusions—Intrauterine exposure to diabetes or obesity is associated with greater offspring insulin resistance than non-exposure, supporting the hypothesis that fetal overnutrition results in metabolic abnormalities during childhood and adolescence.

Accepted Correspondence to: Katherine Sauder. katherine.sauder@ucdenver.edu.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Competing interests

None declared.

Introduction

The prevalence of paediatric Type 2 diabetes in the USA increased by 30% from 2001 to 2008 [1], and 15% of people aged 12–19 years now have diabetes or prediabetes [2]. These trends indicate that diabetes risk begins early in life through a combination of genetic, intrauterine and postnatal environmental exposures. The intrauterine environment appears to be particularly important for the development of early-onset Type 2 diabetes [3]; however, among people aged <20 years, less is known about how intrauterine exposures are related to metabolic abnormalities that are precursors to overt Type 2 diabetes, including insulin resistance and altered insulin secretion. Given that half of women are overweight or obese prior to pregnancy [4] and ≥9% of pregnancies are complicated by maternal diabetes [5] in the USA, a better understanding of how these exposures are associated with offspring diabetes risk is needed to guide early intervention efforts.

The literature reporting independent or combined effects of exposure to maternal diabetes or obesity on offspring glucose/insulin homeostasis is mixed. Several studies have reported increased insulin resistance [6–12], altered β-cell function [11] or reduced disposition index [11, 13] among young people exposed to maternal diabetes *in utero*, but these results may have been confounded by exposure to maternal obesity. Similarly, studies reporting greater insulin resistance among offspring exposed to maternal obesity did not control for maternal diabetes status [14]. The few studies that have evaluated the effects of both maternal diabetes and obesity on offspring glucose/insulin homeostasis report inconsistent results, with some indicating that maternal diabetes predicts outcomes independently of maternal obesity [15–17] or that maternal obesity predicts outcomes independently of maternal diabetes [17], and others reporting no association of these intrauterine exposures with offspring outcomes [18,19]. The literature is also mixed on whether intrauterine exposures have direct effects on glucose/insulin homeostasis [10,11,16], or are mediated, at least in part, through increased offspring body size [11,16,17,20].

The aim of the present analysis was to examine the independent associations of intrauterine exposure to maternal diabetes and obesity with metabolic markers that are precursors for Type 2 diabetes (insulin resistance, β-cell function, oral disposition index) in a longitudinal study of diverse young people. We also explored the degree to which associations were mediated by offspring body size.

Patients and methods

Participants

The Exploring Perinatal Outcomes among Children (EPOCH) study is a longitudinal cohort of offspring recruited from the Kaiser Permanente of Colorado (KPCO) perinatal database. From 2005 to 2010, we recruited children born in singleton pregnancies to mothers who were members of the KPCO health plan and resided in Colorado during the study period. We enrolled children exposed to maternal diabetes *in utero* (n=99), and a random sample of children not exposed to maternal diabetes (n=505). The first research visit (visit 1) occurred at a mean (sd) age among the offspring of 10.4 (1.5) years (n=604). A total of 417 offspring (n=77 exposed, n=340 not exposed) completed a follow-up visit (visit 2) during the period

2010 to 2015 (mean follow-up 6.3 years), at which time the offspring had a mean (sd) age of 16.7 (1.2) years. This study was approved by the Colorado Multiple Institutional Review Board. Mothers provided written informed consent and offspring provided written assent.

Exposures

Maternal diabetes and obesity status were obtained from KPCO medical records. Maternal pre-pregnancy BMI, (kg/m^2) was calculated using the clinically recorded pre-pregnancy weight and height. All pregnant women at KPCO were routinely screened for gestational diabetes (GDM) at 24–28 weeks using the two-step standard protocol [21]. GDM was diagnosed if glucose values exceeded two or more thresholds set by the National Diabetes Data Group on the 3-h, 100-g oral glucose tolerance test [22]. Children were considered to have been exposed to diabetes *in utero* if mothers had Type 1 diabetes or GDM.

Outcomes

Offspring outcomes were evaluated during in-person research visits on the University of Colorado Anschutz Medical Campus. Visit 1 included a fasting venous blood measurement of glucose and insulin. Visit 2 included a 2-h, 75-g oral glucose tolerance test with venous blood measurements at 0, 30 and 120 min. The computer-based homeostatic model was used to calculate insulin resistance [updated homeostatic model assessment of insulin resistance (HOMA2-IR)] and β-cell function [updated homeostatic model assessment of β-cell function (HOMA2-β)] from fasting glucose and insulin values at both research visits (https://www.dtu.ox.ac.uk/homacalculator). The Matsuda index of whole-body insulin sensitivity (Matsuda index) at visit 2 was calculated using glucose and insulin values from the oral glucose tolerance test [23]. The early insulin response was calculated as change in insulin from 0 to 30 min divided by change in glucose from 0 to 30 min. We calculated the oral disposition index, which reflects β-cell function adjusted for insulin resistance, as early insulin response multiplied by the inverse of fasting insulin ($\Delta I_{0–30}/\Delta G_{0–30} \times 1/I_0$) [24].

Covariates

Offspring age was calculated from the date of delivery. Race/ethnicity was self-reported at the first research visit; participants were dichotomized as non-Hispanic white and other. Pubertal development was self-reported by the offspring using diagrammatic representations of Tanner staging, adapted from Marshall and Tanner [25], with staging classified from pubic hair for boys and breast development for girls. Offspring BMI was calculated from height and weight at each visit measured in light indoor clothing without shoes.

Statistical analyses

Analyses were conducted in sas 9.4 (SAS Institute, Cary, NC, USA). Jacknifed, studentized residuals for each model were examined for normality. The outcomes HOMA2-IR, HOMA2-β, and the Matsuda index required natural log transformation prior to analysis to ensure model assumptions were met. Within each visit, we compared offspring who were exposed vs unexposed to maternal diabetes using *t*-tests for continuous variables, a Fisher's exact test for binary categorical variables, and the Cochran–Mantel–Haenszel test for categorical variables with multiple levels.

We fit general linear univariate models (proc glm) for the outcomes which were only measured once (Matsuda index, early insulin response, oral disposition index at visit 2). For outcomes measured at both research visits (HOMA2-IR and HOMA2-β), the repeated measures were included in a single general linear mixed model (proc mixed), with time entered as a repeated effect to account for the correlation between measures within each child. Outcomes were modelled using a three-step procedure. First, separate models were constructed for each exposure of interest (maternal diabetes and pre-pregnancy BMI) predicting each of the offspring outcomes. Second, a combined model was constructed that included both exposures predicting each outcome to determine the independent effects of maternal diabetes and pre-pregnancy BMI. Third, the combined model was further adjusted for offspring BMI to evaluate whether associations of intrauterine exposures with offspring outcomes were mediated by or independent of offspring body size. In a sensitivity analysis, we repeated the above modelling strategy after excluding eight offspring exposed to Type 1 diabetes.

All models were adjusted for offspring sex, race/ethnicity, age and Tanner stage. We also considered a number of two-way interactions: age by Tanner stage (in accordance with previous EPOCH publications [26]), intrauterine exposure (maternal diabetes or pre-pregnancy BMI) by sex, exposure by age, and exposure by Tanner stage. In the combined exposure model, we considered the interaction between maternal diabetes and maternal BMI. In the combined exposure model with offspring BMI, we considered the two-way interactions of offspring BMI with both maternal diabetes and maternal BMI. Non-significant interactions were removed from models. The α value was set at 0.05 for statistical significance. We report β estimates, 95% CIs and *P* values that reflect a status change for exposure to maternal diabetes (exposed vs unexposed) or a 5-kg/m^2 increase in maternal pre-pregnancy BMI. For outcome measures that required natural log-transformation (HOMA2-IR, HOMA2-β and the Matsuda index), we back-transformed the resulting β estimates and 95% CIs. We interpret the β as a multiplicative change in the outcome measure with a change in diabetes exposure status or 5-kg/m^2 increase in maternal BMI (e.g. a back-transformed β estimate of 1.05 indicates a 5% increase in the outcome with a change in exposure status).

Results

Complete data were available for 445 of 604 participants at visit 1 (*n*=155, missing pregnancy BMI; *n*=4, unable to obtain blood; *n*=1, missing Tanner stage) and 299 of the 417 participants who returned for visit 2 (*n*=114, missing pregnancy BMI; *n*=4, unable to obtain blood draw). The analytical sample at visit 1 was similar to the full cohort at visit 1 in terms of offspring age (10.5 vs 10.4 years), BMI (19.0 vs 18.9 kg/m^2), race/ethnicity (43% vs 48% non-Hispanic white), Tanner stage (48% vs 46% stage 1 pre-pubertal), and exposure to maternal diabetes (18% vs 16% exposed). The analytical sample at visit 2 was similar to the full cohort at visit 2 in terms of offspring age (16.5 vs 16.7 years), BMI (23.6 vs 23.6 kg/m^2), race/ethnicity (46 vs 51% non-Hispanic white), Tanner stage (54% vs 54% stage 5 post-pubertal), and exposure to maternal diabetes (21% vs 18% exposed). Participant characteristics at visits 1 and 2, stratified by diabetes exposure group, are reported in Table 1.

In separate exposure models, the age by Tanner stage interaction was statistically significant (P<0.05) for HOMA2-IR and HOMA2-β, and thus retained in all models for these outcomes. The other interactions were non-significant and removed. Exposure to maternal diabetes *in utero* was associated with an 18% increase in HOMA2-IR (P=0.01), a 19% decrease in Matsuda insulin sensitivity (P=0.01), and a 9% increase in HOMA2-β (P=0.04; Table 2). Similar but slightly smaller associations were observed for each 5-kg/m^2 increase in maternal pregnancy BMI (11% increase in HOMA2-IR, P<0.001; 10% decrease in Matsuda insulin sensitivity, P<0.001; 6% increase in HOMA2-β, P<0.001). Neither exposure was associated with the early insulin response or oral disposition index.

In the combined exposure model that included both maternal diabetes and pregnancy BMI, the interaction between these exposures was non-significant for all outcomes and thus removed from all combined models. The association of maternal diabetes with HOMA2-IR and Matsuda remained statistically significant (P=0.04 and 0.03, respectively), while the association with HOMA2-β was attenuated to non-significance (P=0.17; Table 2). The association of maternal BMI with HOMA2-IR, Matsuda insulin sensitivity, and HOMA2-β remained statistically significant (all P<0.001).

In the combined exposure model that additionally included offspring BMI, the interactions of offspring BMI with both maternal diabetes and maternal pre-pregnancy BMI were non-significant and removed. Exposure to maternal diabetes remained significantly associated with a 12% increase in HOMA2-IR (P=0.04) and a 17% decrease in Matsuda insulin sensitivity (P=0.01). By contrast, the association of maternal BMI with HOMA2-IR, Matsuda insulin sensitivity and HOMA2-β were attenuated to non-significance (all P>0.75). Neither exposure was related to the early insulin response or the oral disposition index in the combined model, with or without adjustment for offspring BMI. Similar results were obtained when adjusting for offspring BMI z-score and when using alternate calculations for the early insulin response and oral disposition index (data not shown) [15].

In a sensitivity analysis that included only offspring of women with GDM, similar results were observed (Table S1). In the individual exposure models, both GDM and pregnancy BMI were significantly associated with increased HOMA2-IR, decreased Matsuda insulin sensitivity, and increased HOMA2-β. In the combined exposure model, associations for GDM were attenuated (P=0.08–0.11), while those for pregnancy BMI remained statistically significant (P<0.001). In the final combined model that included current offspring BMI, GDM was associated with 16% lower Matsuda insulin sensitivity (P=0.02) and 8% greater HOMA2-β (P=0.04), although the association for HOMA2-IR was attenuated to non-significance (β=1.11, P=0.06). As in the primary analysis, pregnancy BMI was not associated with offspring outcomes after adjustment for offspring BMI, and neither exposure was related to the early insulin response or the oral disposition index in any model.

Discussion

In this longitudinal study of diverse young people aged 6–19 years, we have shown that intrauterine exposure to maternal diabetes was associated with greater insulin resistance during childhood and adolescence, independently of maternal pre-pregnancy obesity and

offspring BMI. Maternal pre-pregnancy obesity was also associated with markers of insulin resistance and β-cell compensation in offspring, although these effects were attenuated after adjustment for offspring BMI. The present study provides further evidence of the long-term adverse effects of fetal overnutrition on offspring health, and highlights the urgent need for effective diabetes and obesity prevention strategies among women of child-bearing age.

Our findings regarding effects of exposure to maternal diabetes on offspring insulin resistance are consistent with some [6–12,15–17], but not all [13,18,19] previous studies. Greater insulin resistance [6–9,12,15–17] or lower insulin sensitivity [10,11,15] has been reported among offspring aged 4–16 years who were exposed to GDM [6–11,15–17] or Type 1 diabetes [12,15]. Most of these studies [6–12] did not adjust for maternal pre-pregnancy obesity, precluding interpretation of whether these associations were independent of accompanying maternal obesity. Three studies [15–17] have reported an increase in HOMA2-IR among offspring exposed to GDM independent of maternal pre-pregnancy obesity, consistent with the present findings. In two of these studies [15,17], but not the third [16], these associations were also independent of offspring BMI, as in the present analysis, suggesting that adolescent body size does not completely explain the association between maternal diabetes and offspring insulin resistance.

We also provide evidence of β-cell compensation (increased HOMA2-β) among offspring exposed to maternal diabetes, although this association was attenuated to non-significance after adjustment for maternal pre-pregnancy BMI. We did not observe any association between maternal diabetes and offspring oral disposition index assessed with the oral glucose tolerance test during adolescence. In two separate samples of overweight [13] and obese adolescents [11], those who were exposed to GDM had a reduced acute insulin response [13] and a lower oral disposition index [11,13] compared with unexposed offspring. Among young adults aged 18–27 years, Kelstrup *et al.* [15] also reported a lower oral disposition index in offspring exposed to maternal diabetes (Type 1 or gestational) compared with a background population [15]. Recently, Tam *et al.* [27] reported a lower oral disposition index at 7 years in a Chinese cohort of mother–offspring pairs from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. We were unable to replicate these findings in our sample of adolescents aged 16.5 years, of whom only 11% were overweight and 9% were obese. In our cohort, birth weight was similar between exposed and unexposed offspring [26], which suggests that prenatal hyperglycaemia may have been well controlled [28]. In populations with uncontrolled diabetes in pregnancy and excessive fetal growth, the effects of intrauterine exposure to maternal diabetes on offspring glucose/insulin homeostasis may be more prominent; however, given that we did observe increased insulin resistance and an indication of β-cell over-compensation among exposed offspring, it is possible that our exposed participants are developing metabolic dysfunction, but are still in a relatively early stage of disease progression. Clearer differences between exposed and unexposed offspring may emerge as our cohort transitions into young adulthood.

The sensitivity analysis that excluded eight offspring exposed to Type 1 diabetes provided similar results to those of the primary analysis: diabetes exposure was associated with metabolic outcomes independently of maternal and offspring BMI, while associations of

maternal BMI with metabolic outcomes were attenuated to non-significance after adjustment for offspring BMI. We do note the association of GDM exposure with HOMA2-IR was attenuated to non-significance (P=0.06) and the association with HOMA2-β was statistically significant (P=0.04); however, given the similarity of the β estimates between the analyses, our results do indicate that type of diabetes exposure was not a major factor in our analysis, a finding which is in agreement with some [6,8] but not all [29] previous studies. It is plausible that timing and degree of hyperglycaemia in pregnancy may have differential effects on fetal development and thus offspring outcomes. Additional studies that are adequately powered to examine differences between exposure to Type 1 diabetes and GDM are needed to better address this research question.

We found that maternal pre-pregnancy BMI was positively associated with markers of insulin resistance and compensatory insulin secretion in the offspring, independently of maternal diabetes. After further adjustment for offspring BMI, these associations were attenuated to non-significance, suggesting, as expected, that offspring body size is on the causal pathway between maternal BMI and offspring insulin sensitivity. This finding is consistent with data from Project Viva [14] and a Jamaican cohort [20], both of which reported that maternal pre-pregnancy BMI was not related to childhood HOMA2-IR after adjustment for offspring fat mass index [14] or waist circumference [20].

There is a notable lack of studies examining the effects of maternal diabetes and obesity on offspring glucose/insulin homeostasis during puberty, a sensitive period characterized by transient increases in insulin resistance. Davis *et al.* [13] previously reported that adolescents exposed to maternal diabetes had steeper declines in insulin secretion and the oral disposition index as they progressed through puberty compared with unexposed adolescents [13]. In the present analysis, we considered effect modification for both maternal exposures by Tanner stage, but found no evidence that effects differed according to pubertal development. Rather, maternal diabetes was similarly associated with increased insulin resistance across both research visits, independently of Tanner stage and maternal obesity. We do note, however, that Tanner stage was self-reported by participants in our study, and therefore may not be as accurate as when assessed by a trained medical provider. We could not examine the early insulin response and oral disposition index at both research visits because only fasting blood draws were obtained at visit 1 (when ~50% of participants were pre-pubertal). Additional studies that evaluate early insulin response and oral disposition index longitudinally across all pubertal stages are needed to fully evaluate whether the effects of intrauterine exposures vary across puberty.

The present study is limited by the fact that we were unable to conduct stratified analyses by maternal diabetes type to evaluate potential differences related to maternal diabetes type on offspring outcomes. Strengths include the fact that the prospective assessment of offspring outcomes, combined with objective assessment of intrauterine exposures from medical records, allowed us to evaluate the associations of interest without concern for recall bias. A high proportion of participants (approximately two-thirds) returned for visit 2 and did not differ from visit 1 participants in terms of maternal exposures or key offspring characteristics, indicating that preferential loss to follow-up did not occur. We assessed glucose/insulin homeostasis with indices derived from both fasting blood draws and the oral

glucose tolerance test, which have been shown to correlate well with euglycaemic–hyperinsulinaemic clamp-derived indices in people aged 8–20 years [30,31]. Additional strengths of the study include the relatively large sample size, inclusion of ~50% of participants who were from racial/ethnic minorities, and longitudinal multi-level modelling strategy.

In summary, we have shown that fetal overnutrition is associated with metabolic abnormalities that are precursors of Type 2 diabetes in adolescent offspring. Given the high prevalence of obesity and diabetes among women of child-bearing age, a substantial proportion of contemporary children are being exposed to an adverse intrauterine environment with potentially lifelong consequences. Efforts to reduce maternal obesity and prevent maternal diabetes are needed urgently to halt the transgenerational transmission of diabetes and obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- We examined the associations of intrauterine exposure to maternal diabetes and obesity with offspring insulin resistance, β-cell function and oral disposition index.
- Exposure to maternal diabetes was associated with greater insulin resistance in offspring during childhood and adolescence, independently of maternal pre-pregnancy obesity and offspring BMI.
- Maternal pre-pregnancy obesity was associated with insulin resistance and β-cell compensation in offspring, although the effects were attenuated after adjustment for offspring BMI.
- Our study provides further evidence for the long-term adverse effects of fetal overnutrition on offspring health, and highlights the need for effective diabetes and obesity prevention strategies among women of child-bearing age.

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Table 1

Characteristics of EPOCH study participants at each visit according to exposure status

	Visit 1 (*n*=445)			Visit 2 (*n*=299)		
	Exposed (*n*=81)	**Unexposed (*n*=364)**	***P***	**Exposed (*n*=63)**	**Unexposed (*n*=236)**	***P***
Maternal characteristics						
Pre-pregnancy BMI, kg/m^2	27.4 (6.3)	25.4 (5.8)	0.01	27.0 (5.7)	25.5 (6.0)	0.08
Offspring characteristics						
Female	32 (40)	178 (49)	0.14	23 (37)	116 (49)	0.09
Non-Hispanic white	54 (67)	137 (38)	<0.001	43 (68)	96 (41)	<0.001
Age	9.6 (1.7)	10.6 (1.4)	<0.001	15.9 (1.0)	16.6 (1.2)	<0.001
Tanner stage*						
1	52 (64)	162 (45)		0 (0)	0 (0)	
2	18 (22)	115 (32)		0 (0)	2 (1)	
3	8 (10)	64 (18)	0.03	4 (6)	15 (6)	0.90
4	3 (4)	22 (6)		24 (38)	93 (39)	
5	0 (0)	1 (0)		35 (56)	126 (53)	
BMI, kg/m^2	18.8 (4.9)	19.0 (4.4)	0.65	23.2 (5.1)	23.7 (5.7)	0.51
BMI z-score†	0.34 (1.30)	0.29 (1.17)	0.77	0.48 (1.07)	0.43 (1.12)	0.73
Glucose, mmol/l						
Fasting	4.5 (1.3)	4.5 (0.5)	0.76	5.1 (1.3)	5.0 (1.0)	0.33
30-min				7.7 (1.6)	7.4 (1.4)	0.20
120-min				5.4 (1.3)	5.1 (1.2)	0.14
Insulin, pmol/l Fasting‡	55.6 (27.8–90.3)	62.5 (27.8–107.6)	0.06	104.2 (83.3–138.9)	90.3 (69.5–120.0)	0.04
30-min				1073.7 (993.7)	976.3 (806.3)	0.48
120-min				551.5 (688.1)	461.8 (502.1)	0.35
HOMA2-IR‡	0.95 (0.53–1.70)	1.15 (0.53–1.96)	0.07	1.96 (1.56–2.60)	1.68 (1.30–2.31)	0.04
HOMA2-β‡	118.7 (82.1–182.5)	132.7 (92.7–184.8)	0.16	159.5 (126.0–200.5)	147.5 (121.6–175.8)	0.30
Matsuda index‡				6.53 (5.01–9.06)	8.27 (5.73–10.88)	0.05
Early insulin response				438.9 (605.6)	402.6 (785.0)	0.70
Oral disposition index				3.6 (4.6)	3.9 (6.9)	0.74

	Visit 1 (*n*=445)			Visit 2 (*n*=299)		
	Exposed (*n*=81)	**Unexposed (*n*=364)**	***P***	**Exposed (*n*=63)**	**Unexposed (*n*=236)**	***P***
Impaired fasting glucose[§]	0 (0)	8 (2)	0.04	5 (8)	12 (5)	0.41
Fasting glucose in diabetes range[§]	1 (1)	0 (0)		1 (2)	1 (0)	
Impaired glucose tolerance[§]				3 (5)	5 (2)	0.37
Self-reported diabetes diagnosis				1 (2)	1 (90)	0.38

HOMA2-IR, updated homeostatic model of insulin resistance; HOMA2-β, updated homeostatic model of β-cell function.

Values are arithmetic means (sd) or *n* (%), unless otherwise noted.

[*] Self-reported Tanner staging based on pubic hair for boys and breast development for girls.

[†] Age- and sex-specific, calculated with the 2000 Centers for Disease Control growth charts.

[‡] Data are presented as median (interquartile range) due to non-normal distribution. *P* values obtained from *t*-tests on natural log-transformed data.

[§] Impaired fasting glucose defined as 5.6–6.9 mmol/l (100–125 mg/dl); diabetes range defined as ≥7.0 mmol/l; impaired glucose tolerance defined as 120-min glucose 7.8–11.0 mmol/l (1409 mg/dl) [21].

Table 2

Associations of maternal diabetes and pre-pregnancy BMI with offspring glucose/insulin homeostasis

	Maternal Diabetes			Maternal BMI*		
	β	**(95% CI)**	***P***	**β**	**(95% CI)**	***P***
Separate exposure models†						
Insulin resistance/sensitivity						
HOMA2-IR‡	1.18	(1.05, 1.33)	0.01	1.11	(1.07, 1.15)	<0.001
Matsuda‡	0.81	(0.70, 0.95)	0.01	0.90	(0.85, 0.95)	<0.001
β-cell function						
HOMA2-β‡	1.09	(1.003, 1.18)	0.04	1.06	(1.03, 1.09)	<0.001
Early insulin response (pmol/mmol)	38.6	(−193.1, 270.2)	0.74	9.9	(−67.1, 86.9)	0.80
Oral disposition index (mM^{-1})	−0.22	(−2.22, 1.77)	0.83	−0.30	(−0.96, 0.37)	0.38
Combined exposure model§						
Insulin resistance/sensitivity						
HOMA2-IR‡	1.13	(1.01, 1.27)	0.04	1.10	(1.06, 1.14)	<0.001
Matsuda‡	0.84	(0.72, 0.98)	0.03	0.90	(0.86, 0.95)	<0.001
β-cell function						
HOMA2-β‡	1.06	(0.98, 1.15)	0.17	1.06	(1.03, 1.09)	<0.001
Early insulin response (pmol/mmol)	35.4	(−198.6, 269.3)	0.77	8.4	(−69.3, 86.2)	0.83
Oral disposition index (mM^{-1})	−0.11	(−2.13, 1.90)	0.91	−0.29	(−0.96, 0.38)	0.39
Combined exposure model adjusted for offspring BMI§						
Insulin resistance/sensitivity						
HOMA2-IR‡	1.12	(1.01, 1.24)	0.03	1.00	(0.97, 1.04)	0.95
Matsuda‡	0.83	(0.72, 0.95)	0.01	0.99	(0.94, 1.04)	0.77
β-cell function						
HOMA2-β‡	1.06	(0.98, 1.14)	0.14	1.00	(0.98, 1.03)	0.90
Early insulin response (pmol/mmol)	43.8	(−189.1, 276.6)	0.71	−29.1	(−114.8, 56.7)	0.51
Oral disposition index (mM^{-1})	−0.11	(−2.12, 1.91)	0.92	−0.32	(−1.06, 0.42)	0.40

HOMA2-IR, updated homeostatic model of insulin resistance; HOMA2-β, updated homeostatic model of β-cell function.

Results for HOMA2-IR and HOMA2-β include repeated measurements collected on the same individuals at visit 1 and visit 2. Results for Matsuda, early insulin response, and oral disposition index include measurements collected at visit 2 only.

[*] Per 5 kg/m^2 increase in maternal pregnancy BMI.

[†] Models constructed separately for maternal diabetes and obesity. Models are adjusted for offspring sex, race/ethnicity, age, Tanner stage, and for HOMA2-IR and HOMA2-β only, age by Tanner interaction.

[‡] Data were natural log-transformed for analysis; interpret β as percentage change in outcome with status change in maternal diabetes exposure and 5-kg/m^2 increase in maternal pregnancy BMI.

[§] Single model constructed with both maternal diabetes and obesity as predictors. Model is also adjusted for offspring sex, race/ethnicity, age, Tanner stage, age by Tanner interaction.