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Association between gestational diabetes mellitus exposure and childhood adiposity is not substantially explained by offspring genetic risk of obesity

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Abstract

Aim—To examine the extent to which offspring obesity-associated genetic risk explains the association between gestational diabetes mellitus and childhood adiposity.

Methods—We studied 282 children aged 7–12 years who were enrolled in the Exploring Perinatal Outcomes in Children Study. A genetic risk score for BMI was calculated as the count of 91 established BMI-raising risk alleles. Multivariable linear and logistic regression models were used to estimate associations between the offspring genetic risk score and exposure to gestational diabetes and childhood adiposity (BMI and waist circumference), adjusting for clinical and demographic covariates. The contribution of offspring genetic risk to associations between maternal gestational diabetes and childhood outcomes was estimated by comparing the regression coefficients for the gestational diabetes variable in models with and without the genetic risk score.

Results—The offspring BMI genetic risk score was associated with childhood BMI ($P=0.006$) and waist circumference ($P=0.02$), and marginally with gestational diabetes ($P=0.05$). Offspring BMI genetic risk did not contribute significantly to associations between gestational diabetes and childhood BMI [7.7% (95% CI –3.3, 18.8)] or waist circumference [5.8% (95% CI –3.1, 14.8); $P=0.2$ for both].

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Competing interests
None declared.

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

Conclusions—Offspring obesity genetic risk does not explain a significant proportion of the association between gestational diabetes exposure and childhood adiposity. The association between gestational diabetes and childhood adiposity is probably explained through alternative pathways, including direct intrauterine effects or a shared postnatal environment.

Introduction

Obesity is a growing public health problem globally, and childhood obesity in particular portends an increasing burden of cardiovascular disease and diabetes worldwide [1–4]. Obesity is highly heritable, and recent large studies have yielded nearly 100 independent loci associated with obesity [5,6]. In addition to genetic transmission of obesity risk, prior work has shown that intrauterine exposures, including exposure to maternal diabetes, hyperglycaemia and obesity, can influence offspring obesity risk [7–11]. Gestational diabetes mellitus (GDM) represents a well-defined intrauterine exposure associated with offspring adiposity [7,8,11]. The association between GDM and offspring adiposity can be attributed to shared genetics between mother and child, the programming effects of intrauterine exposure to hyperglycaemia, and postnatal health behaviours shared by mother and child (Fig. S1). The relative contributions of each of these pathways to the association between GDM exposure and childhood adiposity is unknown. Accordingly, the aim of the present study was to estimate the extent to which obesity-associated offspring genetic variants explain the association between maternal GDM exposure *in utero* and childhood adiposity.

Methods

Study population

The Exploring Perinatal Outcomes in Children (EPOCH) cohort study has been described previously [7,8]. Briefly, the EPOCH cohort is a historical prospective cohort that enrolled children aged 7–12 years who were exposed ($n=100$) and not exposed ($n=504$) to GDM during singleton pregnancies, born to mothers who were members of the Kaiser Permanente of Colorado (KPCO) Health Plan. From the original cohort, a subset of 82 exposed children and 200 frequency-matched (for age, sex and race/ethnicity) unexposed children who consented to genotyping were included in this study. Maternal pre-pregnancy data, birth weight and gestational age at birth were collected from the electronic health records of the KPCO. The study was approved by the Colorado Multiple Institutional Review Board; all mothers provided written informed consent, and children provided written assent.

Genetic risk

DNA was extracted from peripheral venous blood drawn from offspring at the study visit using standard protocols. Genotyping was performed on the Illumina Omni 2.5 platform, and only samples with a call rate exceeding 98% were retained for analysis. Individuals with discordance between reported and genotyped sex, or with a high degree of heterozygosity were excluded. To calculate the offspring obesity genetic risk score, we used 91 single nucleotide polymorphisms (SNPs) or proxies (Table S1) previously associated with BMI at the genome-wide significance level [5,6]. The genetic risk score was the sum of risk alleles (0, 1 or 2) at each locus. Previous analysis of childhood BMI using a genetic risk score for

BMI has shown that unweighted and weighted scores yielded similar results, so we opted to use an unweighted score in the present study [12]. For individuals with missing genotype at an allele, we assigned the expected value for that allele based on allele frequency in our study population.

Exposures

The primary exposure, GDM, was derived from the KPCO electronic health database. All pregnant KPCO beneficiaries who did not have diabetes underwent standard two-step GDM screening at 24–28 weeks' gestation (first step: 1-h 50-g oral glucose tolerance test; second step: 3-h 100-g oral glucose tolerance test), and GDM exposure was deemed to be present if two or more blood glucose values during the second step oral glucose tolerance test exceeded the National Diabetes Data Group criteria for positivity [8,13].

Outcomes

Our primary outcomes were childhood BMI and waist circumference at the study visit. The measurement of each of these outcomes has been described previously [8]. Briefly, BMI was calculated using height and weight measured in light clothing while not wearing shoes, while waist circumference measurements followed National Health and Nutrition Examination Survey protocols [14]. Standardized protocols were followed by trained research staff for all measurements.

Statistical analysis

Child and maternal demographic and anthropometric variables, as well as child obesity genetic risk score, in those exposed vs those unexposed to GDM were compared using chi-squared tests for categorical data and Mann–Whitney Wilcoxon non-parametric tests for continuous or ordinal data. We used three successive modelling steps to estimate the proportions of the exposure–outcome associations explained by the obesity genetic risk score. First, we used logistic regression to estimate the association between the offspring obesity genetic risk score and maternal GDM, adjusting for maternal age and child race. Secondly, we used generalized linear models to estimate the associations between genetic risk and both measures of childhood adiposity, adjusting for child's age, race, sex, birth weight, Tanner stage, and interaction between age and Tanner stage. Finally, we compared the association between maternal GDM and measures of childhood adiposity in models both without and with the genetic risk score as a covariate, adjusting all models for child's age, race, sex, birth weight, Tanner stage, and interaction between age and Tanner stage. The covariates selected for the present analysis were found to be associated with GDM exposure and measures of offspring adiposity in a previous study establishing the association between GDM and offspring adiposity in the EPOCH cohort [8]. Notably, this previous study also found that other potential confounders, including socio-economic factors, offspring physical activity and caloric intake, and markers of intrauterine growth, did not have a substantial impact on the association between GDM and offspring adiposity. As the goal of the present study was to estimate the contribution of obesity genetic risk to the association between GDM and childhood adiposity that had previously been studied in the EPOCH cohort, we adopted the same covariates/models as those used previously [8]. The proportion of the exposure–outcome association explained by genetic risk was estimated as the difference in β

coefficients for exposure between the models with and without the genetic risk score divided by the exposure β coefficient from the model without the genetic risk score. Confidence intervals (CIs) for the proportion explained were estimated using the delta method, as previously described [15]. All analyses were performed in SAS 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Table 1 shows the maternal and child characteristics at the time of birth and at the study visit. The 82 participants exposed to GDM and 200 unexposed individuals were similar with regard to birth weight and gestational age at birth, as well as the burden of obesity genetic risk alleles (Table 1). Mothers with GDM had higher pre-pregnancy BMI, higher BMI at the study visit, and were older at the time of birth compared with those without GDM (Table 1).

The offspring obesity genetic risk score was weakly associated with maternal GDM [odds ratio 1.05 (CI 1.00, 1.10); $P=0.05$ (Table S2)] and maternal pre-pregnancy overweight/obesity [odds ratio 1.11 (CI 1.04, 1.18); $P=0.001$ (Table S2)]. Similarly, obesity genetic risk was associated with childhood BMI and waist circumference [$\beta=0.11$, $P=0.006$ for BMI; $\beta=0.27$, $P=0.02$ for waist circumference (Table S3)]. Finally, we examined the association between *in utero* exposure and childhood adiposity outcomes. As previously shown, maternal GDM was strongly associated with childhood BMI and waist circumference (Table 2). The association between GDM and childhood adiposity was not significantly reduced with the inclusion of the offspring obesity genetic risk score as a covariate (Table 2). Child obesity genetic risk did not contribute significantly to the GDM–BMI (7.7% [95% CI –3.3, 18.8], $P=0.2$) or GDM–waist circumference associations [5.8% (95% CI –3.1, 14.8); $P=0.2$]. We tested the sensitivity of our results to model specification by repeating the analysis in unadjusted models and in models adjusted for only age, sex and race. The contribution of the obesity genetic risk score to the GDM–BMI and GDM–waist circumference associations did not vary substantially across different model specifications (Table S4).

Discussion

In the present study, we examined the extent to which offspring genetic risk of obesity explains the association between intrauterine exposure to GDM and childhood adiposity. The obesity genetic risk score was associated with maternal GDM, as well as childhood BMI and waist circumference; however, there was no significant evidence that obesity genetic risk contributed to the associations between GDM exposure and childhood adiposity. Discriminating between mechanisms involving obesogenic genotype, postnatal environment, and direct intrauterine effects is important for enhancing our biological understanding of obesity development and for guiding the approach to behaviour modification interventions aimed at reducing childhood obesity. Our results suggest that offspring inheritance of obesity risk alleles (where half are from the mother) does not explain the association between *in utero* GDM exposure and the development of obesity, and support a role for direct intrauterine effects and/or shared postnatal behaviours in mediating the GDM–childhood adiposity association.

This study, examining offspring genetic risk of obesity, complements other recent studies that examine maternal genetic variants to dissect the genetic and environmental influences on the association between maternal and offspring BMI. For example, a family-based study has suggested that shared genetics, environment and behaviours may play a more important role than intrauterine exposures in familial clustering of obesity [16]. Consistent with the present findings, previously published genetic instrumental variable analyses did not support a causal association between genetically estimated maternal BMI levels and offspring adiposity later in childhood [17,18]. The present study extends the previous work by suggesting that the association between maternal GDM (rather than maternal BMI) and childhood adiposity may be driven by direct intrauterine effects and a shared postnatal environment to a greater extent than simply through shared obesity-associated genetic variants.

The present study has several limitations. First, as maternal genetic data were unavailable, we were unable to discriminate between maternal and paternal contributions to the offspring genetic risk score. This could cause overestimation of the influence of offspring genetic risk on the association between GDM and offspring adiposity. Second, our sample size is relatively small compared with many genetic studies of complex metabolic traits; however, we were able to detect associations between the offspring obesity genetic risk score and both maternal GDM and childhood adiposity, which ensured that we could at least nominally evaluate the obesity genetic risk score as an intermediate variable, albeit with limited power. Third, our data are derived from a narrow geographic context, with mothers all receiving care in a single health system. Finally, the study is limited by the degree to which the alleles included in the genetic risk score capture the heritability of adiposity.

Despite these limitations, the results of the present study suggest that obesity-associated genetic risk alleles do not contribute substantially to the association between *in utero* exposure to GDM and childhood adiposity. These results imply that interventions targeting gestational weight gain and GDM, as well as healthy postnatal behaviour and environment, could positively impact transmission of obesity across generations, irrespective of underlying genetic risk. Further work is needed to better understand the mechanisms through which intrauterine exposures promote childhood adiposity and to develop effective preventive interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- It is not known whether the association between maternal gestational diabetes mellitus and offspring adiposity in childhood is attributable to shared obesogenic genetics, postnatal environment or direct intrauterine effects of hyperglycaemia. The Exploring Perinatal Outcomes in Children Study is an observational cohort study that assessed maternal–child dyads from pregnancies complicated by gestational diabetes and used offspring common variant genotyping to investigate offspring genetic contributions to associations between gestational diabetes and childhood outcomes.
- Common obesity genetic risk variants in offspring explain only a minor proportion of the association between maternal gestational diabetes and offspring childhood adiposity.

Table 1

Study participant characteristics

	Exposed to GDM (<i>n</i> =82)		Not exposed to GDM (<i>n</i> =200)		<i>P</i>
	Mean (SD)	<i>n</i> (%)	Mean (SD)	<i>n</i> (%)	
Mothers					
Age at delivery, years	33.5 (5.4)	-	30.8 (5.2)	-	0.0002
Pre-pregnancy BMI, kg/m ²	27.9 (6.3)	-	24.4 (4.7)	-	<0.0001
BMI at study visit, kg/m ²	30.6 (7.1)	-	27.3 (6.3)	-	<0.0001
Children					
Sex					0.80
Male	-	43 (48)	-	100 (50)	
Female	-	39 (52)	-	100 (50)	
Race					0.80
White	-	54 (66)	-	124 (62)	
Black	-	3 (4)	-	7 (4)	
Hispanic	-	21 (26)	-	62 (31)	
Other	-	4 (5)	-	7 (4)	
Gestational age at birth, weeks	38.9 (1.6)	-	39.1 (1.7)	-	0.13
Birth weight, g	3353 (536)	-	3368 (458)	-	0.92
Age at study visit, years	9.6 (1.7)	-	10.2 (1.3)	-	0.001
BMI at study visit, kg/m ²	19.1 (4.7)	-	18.2 (3.7)	-	0.18
Tanner stage at study visit					0.007
1	-	58 (71)	-	103 (52)	
2	-	14 (17)	-	76 (38)	
3	-	6 (7)	-	14 (7)	
4	-	3 (4)	-	6 (3)	
5	-	1 (1)	-	0 (0)	
Genetic risk score					
Obesity	87.7 (5.4)	-	86.3 (5.6)	-	0.04

GDM, gestational diabetes mellitus.

Table 2

Proportion of association between maternal gestational diabetes and offspring adiposity explained by offspring obesity genetic risk score

Exposure	Outcome	Intermediate variable	β^* (95% CI)	Proportion explained, % (95% CI)
GDM	Child BMI	None	1.72 (0.70, 2.74)	-
		Obesity GRS ^b	1.59 (0.57, 2.61)	7.7 (-3.3, 18.8)
	Child waist circumference	None	5.26 (2.46, 8.06)	-
		Obesity GRS ^b	4.96 (2.16, 7.75)	5.8 (-3.1, 14.8)

GDM, gestational diabetes mellitus; GRS, genetic risk score.

* β coefficient (in kg/m² for child BMI and cm for child waist circumference) for association between exposure and outcome in models without and with the intermediate variable.