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GLP-1R Polymorphisms Modify the Relationship Between Exposure to Gestational Diabetes and Offspring BMI Growth: The EPOCH Study

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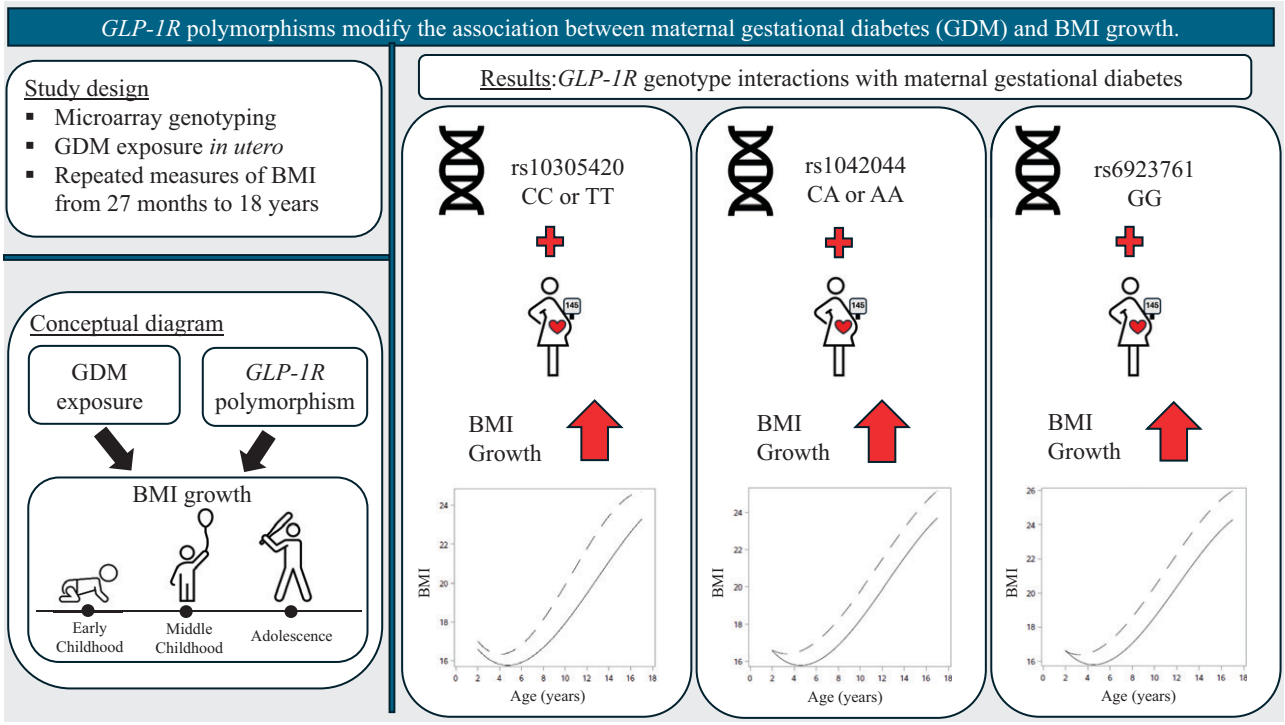

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We wished to test whether *GLP-1R* polymorphisms enhance the association of exposure to maternal gestational diabetes mellitus (GDM) on offspring BMI growth and surrogate markers of glucose-insulin homeostasis.

- **What is the specific question we wanted to answer?**
  We asked whether, in youth, *GLP-1R* polymorphisms modify the associations between *1*) GDM and BMI growth and *2*) GDM and surrogate markers of glucose-insulin homeostasis.

- **What did we find?**
  GLP-1R polymorphisms modify the association between GDM and BMI growth across childhood and adolescence, but not the associations between GDM and surrogate markers for glucose-insulin homeostasis.

- **What are the implications of our findings?**
  GLP-1R polymorphisms may spotlight children who are at the highest risk for rapid BMI growth, and assist clinicians with defining populations in need of intervention.

GLP-1R Polymorphisms Modify the Relationship Between Exposure to Gestational Diabetes and Offspring BMI Growth: The EPOCH Study

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Kylie K. Harrall,[1,2,3] Deborah H. Glueck,[4] Leslie A. Lange,[3,5] Elizabeth M. Litkowski,[5,6] Lauren A. Vanderlinden,[7] Iain R. Konigsberg,[5] Melanie G. Cree,[8] Wei Perng,[1,3] and Dana Dabelea[1,3,4]

OBJECTIVE

Exposure to maternal gestational diabetes mellitus (GDM) is associated with childhood BMI. Among youth, we explored whether three different glucagon-like peptide 1 receptor gene (*GLP-1R*) polymorphisms modified the associations between *1*) GDM and BMI trajectories and *2*) GDM and markers of glucose-insulin homeostasis.

RESEARCH DESIGN AND METHODS

For 464 participants from the Exploring Perinatal Outcomes Among Children (EPOCH) study, microarray genotyping was performed during childhood (∼10 years). BMI trajectories across childhood and adolescence were characterized using repeated measurements from research visits and medical record abstraction. Markers of glucose-insulin homeostasis were derived from one oral glucose tolerance test in adolescence (∼16 years). Linear models assessed effect modification by *GLP-1R* polymorphisms.

RESULTS

Among youth with at least one minor allele of rs10305420 (CT or TT) or rs1042044 (CA or AA), but not among major allele homozygotes, exposure to GDM was associated with higher average BMI. For rs6923761, participants who were exposed to GDM and were major allele homozygotes (i.e., genotype GG) had significantly higher average BMI than all other participants in the cohort. No polymorphisms modified the association between GDM and markers of glucose-insulin homeostasis during adolescence.

CONCLUSIONS

***GLP-1R* polymorphisms modify the association between GDM and BMI growth among youth. Further studies are needed to replicate these findings, and to better understand the mechanisms by which *GLP-1R* polymorphisms lead to heterogeneity in offspring BMI growth.**

Gestational diabetes (GDM) is increasing in the U.S., affecting between 2 and 10% of women during pregnancy (1). Offspring of women exposed to GDM during pregnancy are more likely to experience higher BMI and obesity during childhood (2,3) and adolescence (4,5). Children exposed to GDM are also more likely to experience faster rates of BMI growth, an indicator of higher fat mass accrual than those

[1]Lifecourse Epidemiology of Adiposity and Diabetes Center, University of Colorado Anschutz Medical Campus, Aurora, CO
[2]Department of Health Outcomes and Biomedical Informatics, University of Florida College of Medicine, Gainesville, FL
[3]Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO
[4]Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO
[5]Department of Biomedical Informatics, University of Colorado School of Medicine, Aurora, CO
[6]Department of Neurology, The University of Michigan, Ann Arbor, MI
[7]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO
[8]Division of Pediatric Endocrinology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

Corresponding author: Kylie K. Harrall, kylie.harrall@ufl.edu

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unexposed (6,7). GDM-associated differences in offspring BMI growth appear during middle childhood and persist throughout adolescence (7).

Exposure to maternal GDM has also been associated with offspring abnormalities in markers of glucose-insulin homeostasis. In the Exploring Perinatal Outcomes Among Children (EPOCH) cohort, the cohort studied in this manuscript, children (8) exposed to GDM had higher estimated insulin resistance (HOMA2-IR and Matsuda index) and compensatory β-cell secretion (HOMA2-%B) during childhood than peers without exposure. The association between GDM exposure and offspring childhood insulin resistance has been consistently replicated across cohorts (9,10). Exposure to GDM has also been associated with higher fasting and stimulated glucose levels during oral glucose tolerance testing (OGTT) (9) and lower oral disposition index (10).

While there is strong evidence that GDM exposure is associated with increased childhood BMI growth and altered glucose-insulin homeostasis, some studies have found null associations (11–13). This suggests that there may be heterogeneity in the effects of exposure to maternal GDM on offspring growth and metabolic health. Heterogeneity likely occurs because both genetic susceptibility and environmental risk factors influence these outcomes. This was illustrated by Stanislawski et al. (14), who showed, in the EPOCH cohort, that the associations of a type 2 diabetes genetic risk score with fasting and stimulated glucose levels from OGTT were modified by exposure to GDM in utero.

Common polymorphisms of the glucagon-like peptide 1 receptor (GLP-1R) have been associated with both BMI and markers of glucose-insulin homeostasis in children. Previously, we showed that participants who were major allele homozygotes for *GLP-1R* polymorphism rs6923761 (genotype GG) had higher BMI growth across childhood and adolescence and higher estimated insulin resistance (15). Participants who were major allele homozygotes for *GLP-1R* polymorphism rs10305420 (genotype CC) had significantly higher estimated insulin resistance and insulin secretion when compared with participants with the minor allele. However, we did not consider interactions between *GLP-1R* polymorphisms and exposure to maternal gestational diabetes, which is important given that in utero programming of metabolic risk is now recognized as an important contributor to early-life manifestations of obesity and type 2 diabetes (16). We considered these interactions in the current manuscript.

GLP-1R polymorphisms play a role in glucose-insulin homeostasis and eating behaviors. Binding between glucagon-like peptide 1 (GLP-1) and orthosteric GLP-1R initiates glucose-dependent insulin biosynthesis and secretion from the pancreatic β-cells, and inhibits glucagon secretion from the pancreatic α-cells (17). Although predominately found in the pancreas, GLP-1R has been found in many tissues throughout the body (18). In the brain, it is believed that binding between GLP-1 and GLP-1R assists with regulation of appetite and eating behavior. In the gastrointestinal system, interaction between the peptide and receptor assists with regulating gastric emptying.

The aims of this manuscript were to assess whether *GLP-1R* polymorphisms, maternal GDM, and their interaction were associated with *1*) offspring BMI growth and *2*) markers of glucose-insulin homeostasis. Our hypotheses were that *GLP-1R* polymorphisms would be associated with further increases in BMI growth and worsened glucose-insulin homeostasis.

RESEARCH DESIGN AND METHODS

Study Population

The EPOCH study is a historical prospective study in Denver, CO. The study recruited 604 mother/child dyads from the Kaiser Permanente of Colorado Health system (KPCO). Recruitment details appear elsewhere (6). The EPOCH study aimed to understand how in utero exposure to maternal GDM influences metabolic outcomes among offspring. The study oversampled children who were exposed to GDM, such that 15% of the final cohort had exposure. Children were asked to complete two research visits: *1*) during childhood at ~10 years of age and *2*) during adolescence at ~16 years of age. Participants were eligible for this analysis if they had genotyping data and at least one outcome measurement (n = 464). Mothers provided written consent, and children provided verbal assent, prior to the first visit. The Colorado Multiple Institutional Review Board (Aurora, CO; protocol no. 05-0623) approved the study.

Assessment of In Utero Exposure to GDM

Maternal GDM diagnosis was extracted from KPCO medical records. KPCO performed routine screening for GDM among pregnant women between 24 and 28 weeks of gestation. Screening involved a two-step glucose challenge protocol: all women were screened with a 1-h 50-g glucose challenge test. If routine screening was positive, GDM status was confirmed with a 3-h 100-g glucose challenge test (19,20).

Genotyping and Imputation of GLP-1 Receptor Variants

Genotyping was conducted from venous blood. Blood samples were stored at −80°C, with DNA isolation and purification as previously described (21). The first set of samples (n = 336) were genotyped on the Illumina Infinium Omni2.5-8 v1.1 BeadChip (Illumina, San Diego, CA). Genotypes were filtered to variants located at the same chromosomal and base pair positions present on the Omni2.5-8 v1.4 array. The second set of samples (n = 140) were genotyped on the Illumina Multi-Ethnic Global Array v1.0. Both arrays were combined for analysis. Genetic ancestry and batch effects were assessed using genotypes that were directly measured and passed quality control on both arrays.

This report focuses on three previously studied (22) *GLP-1R* missense polymorphisms in linkage equilibrium with minor allele frequency >5% in EPOCH: rs10305420, rs6923761, and rs1042044. The amino acid substitutions for these three variants are rs10305420 (c.20C>T) resulting in a Pro→Leu change; rs6923761 (c.502G>A) resulting in a Gly→Ser change; and rs1042044 (c.780A>C) resulting in a Phe→Leu change.

While genotypes for rs6923761 and rs1042044 were directly measured on each array using probe technology, rs10305420 was imputed, because neither assay included a probe that targeted the polymorphism. Separately for each array, imputation was performed using the Michigan Imputation Server (v1.0.4) with Eagle v2.5 phasing and the 1000 Genomes Phase 3 (v5) reference panel. For rs10305420, imputed genotypes were estimated as continuous dosage values ranging from 0 to 2, which were highly clustered around 0, 1, and 2 (Fig. 1). These results are similar to those obtained through direct genotyping. The dosage for rs10305420 was categorized as 0 for values <0.5, 1 for values ≥0.5 and <1.5, and 2 for values ≥1.5.

Statistical models assumed dominant effect coding for each *GLP-1R* polymorphism,

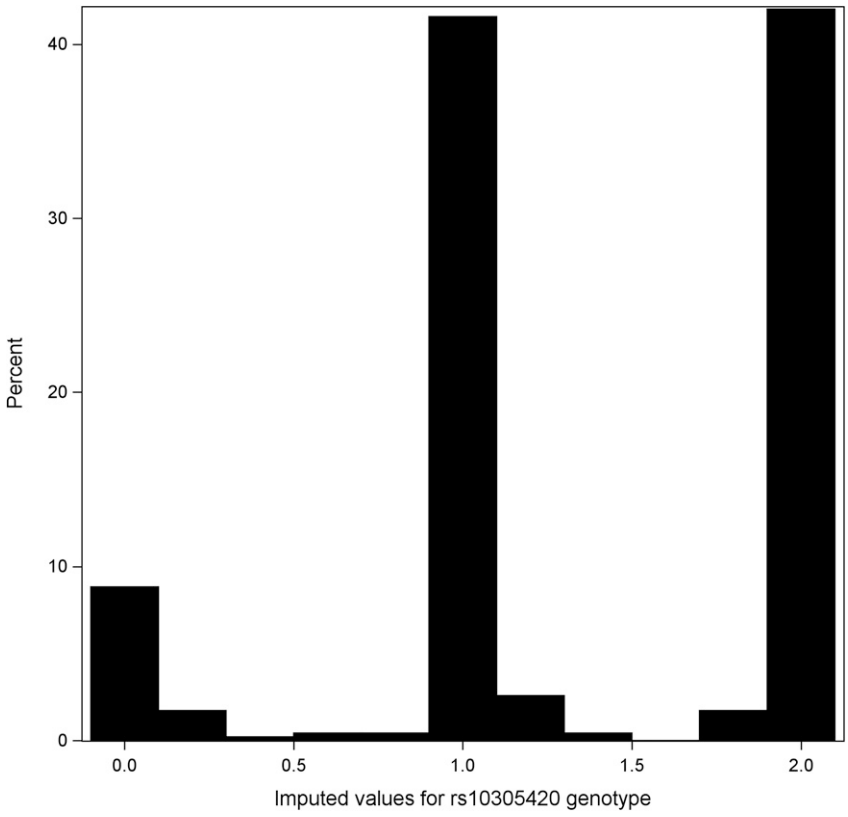

Figure 1—Distribution of imputed dosages for *GLP-1R* polymorphism rs10305420.

which allows for comparison of the homozygous major allele genotype to at least one copy of the minor allele. While studies of polymorphisms often assess risk associated with the minor allele, studies of rs10305420, rs6923761, and rs1042044 have consistently shown that risk is associated with homozygous major genotypes (23–25). Separate indicator variables represented the major homozygous genotype as 0, and the presence of at least one minor allele as 1.

Assessment of BMI Across Childhood and Adolescence

Repeated measurements of BMI were calculated as weight in kilograms divided by height in meters squared (kg/m^2). At EPOCH research visits, height was measured using a portable Seca stadiometer (Chino, CA), and weight was measured using a portable electronic Seca scale (Chino, CA). Additional measurements of height and weight were abstracted from KPCO medical records from age 27 months to the end of EPOCH follow-up, with a maximum age of 19 years. Among 584 participants, 73% had nine or more repeated measurements of height and weight. Height and weight trajectories were cleaned using a validated algorithm (26) designed to remove anomalous values from pediatric growth data.

Surrogate Markers of Glucose-Insulin Homeostasis

Two-hour, 75-g OGTT were performed at the second EPOCH research visit during adolescence (n = 387). Concentrations of glucose and insulin were measured from venous blood draws collected at 0, 30, and 120 min. Enzymatic kits and an AU400e chemistry analyzer were used to measure glucose concentration. Radioimmunoassay (Millipore, Darmstadt, Germany) was used to measure insulin concentration.

Insulin sensitivity (HOMA2-IR) and secretion (HOMA2-%B) were estimated using a homeostasis model of assessment calculator (27). Insulinogenic index and β-cell function were calculated using baseline and 30-min post–glucose challenge measurements from OGTT. Insulinogenic index was computed as $[(\text{Insulin}_{0\text{minutes}} - \text{Insulin}_{30\text{minutes}})/(\text{Glucose}_{0\text{minutes}} - \text{Glucose}_{30\text{minutes}})]$. Oral disposition index was computed as [insulinogenic index × $(1/\text{insulin}_{0\text{minutes}})$].

Assessment of Model Covariates

Demographic information was collected by self-report. Participants self-reported biological sex assigned at birth. Self-identified race and ethnicity, which is viewed as a social construct, was categorized as Hispanic or one of three non-Hispanic categories, including White, Black, and other. Age was calculated as differences with date of birth.

Statistical Analyses

Continuous variables were assessed as mean and SD, and categorical variables were assessed as number and percent. The t tests, χ^2 test, or Fisher exact test were used to test for differences by genotype category.

Models of BMI Trajectories Across Childhood and Adolescence

Separately for each polymorphism, we fit general linear mixed models to assess effect modification. The outcome was repeated measurements of BMI. The predictors were polynomials of age (age, age^2, and age^3), an indicator variable for at least one copy of the *GLP-1R* minor allele, an indicator variable for GDM, and the two- and three-way interactions between each age polynomial and the indicator variable for *GLP-1R* or GDM. The highest-order term considered was cubic, mirroring the shape of the curve described by Hockett et al. (7). The models were additionally adjusted for sex and the first three genetic principal components (21). Random intercepts and slopes, with unstructured covariance between the random effects, accounted for increasing variance of BMI with age and within participant correlation.

For each polymorphism considered, a similar approach was used. First, a planned series of likelihood ratio tests were used to find the best-fitting model, assessing, and removing if not significant at the 0.05 level, interactive terms, in order from highest to lowest. Then, in the best-fitting model, associations between the polymorphism, GDM, and the trajectory were assessed.

First, we tested whether the *GLP-1R* polymorphism modified the association between GDM and the BMI trajectory, using a multiple degree of freedom chunk test. Second, we tested the hypothesis that *GLP-1R* polymorphism modified the association between GDM and velocity of BMI growth. Model assumptions were assessed using jackknife studentized residuals. Significance was determined using the Wald test with Kenward-Roger (28)

degrees of freedom and an α-level of 0.05. Age-specific estimates, 95% CIs, F statistics, and *P* values were reported for each association of interest. Figures were used to describe the population line for each population subset, cross-classified by in utero GDM exposure, and each *GLP-1R* polymorphism status.

Models of Insulin Sensitivity, Insulin Secretion, and β-Cell Function

Separate general linear models assessed whether each *GLP-1R* polymorphism modified the association between exposure to GDM and each surrogate marker of glucose-insulin homeostasis. Outcomes included the natural logs of HOMA2-IR and HOMA2-%B, insulinogenic index, and oral disposition index. The predictors included an indicator variable for *GLP-1R*, an indicator variable for exposure to GDM, and an interaction between *GLP-1R* and exposure to GDM. Models were adjusted for sex, age at EPOCH visit 2, and the first three genetic principal components (21). Jackknife studentized residuals were visualized to assess model assumptions. Significance was determined using an α-level of 0.05. β-estimates and 95% CIs were reported for each association.

Data and Resource Availability

Deidentified data from the EPOCH study may be made available, upon reasonable request.

RESULTS

Participant characteristics are shown in Table 1. There were 464 participants included in the analyses. The frequency of participants who were major allele homozygotes was 43% for rs10305420, 53% for rs6923761, and 31% for rs1042044. The proportion of female participants who were major allele homozygotes were as follows: rs10305420: 49%; rs6923761: 55%; and rs1042044: 45%. For all three polymorphisms, there were significant differences in self-identified race and ethnicity by genotype. Additionally, rs10305420 CC genotypes were more likely to have GDM exposure than participants with the minor allele (23% and 15%, respectively).

rs10305420

BMI Growth

As shown in Supplementary Table 1, rs10305420 modified the association between GDM and BMI growth across childhood and adolescence, including the trajectory of BMI growth ($P < 0.0001$) and the velocity of BMI growth ($P < 0.0001$). More about the velocity analysis, including estimates of direction and magnitude, appears in Supplementary Results 1. Relationships are shown visually in Fig. 2. Exposure to GDM was associated with a higher average BMI across follow-up from ages 6 to 15 years. The association was most pronounced among individuals with a minor allele (i.e., genotype CT or TT). Participants with the minor allele and with GDM exposure had higher average BMI across follow-up when compared with individuals with the minor allele and without GDM exposure. For example, at the age of 10 years, participants with the minor allele and with GDM exposure had 1.97 kg/m^2 (95% CI: 0.76, 3.18) higher average BMI than participants with the minor allele and without GDM exposure. Among major allele homozygotes, there were no differences in BMI growth at any age when comparing participants with and without GDM exposure.

Surrogate Markers of Glucose-Insulin Homeostasis

rs10305420 did not modify associations of GDM with glucose or insulin levels across OGTT or with surrogate markers for glucose-insulin homeostasis (all interaction *P* values >0.05) (Table 2).

rs6923761

BMI Growth

As shown in Supplementary Table 2, rs6923761 modified the association between GDM and BMI growth across childhood and adolescence, including the trajectory of BMI growth ($P = 0.0036$) and the velocity of BMI growth ($P = 0.0027$). More about the velocity analysis, including estimates of direction and magnitude, appears in Supplementary Results 1. Relationships are shown visually in Fig. 2. Exposure to GDM was associated with higher average BMI. However, this association was most pronounced among participants who were major allele homozygotes for rs6923761 (i.e., genotype GG). Major allele homozygotes with GDM exposure had higher average BMI across childhood and adolescence compared with all other groups. For example, for participants at age 10 years, major allele homozygotes with GDM exposure had a higher average

Table 1—Characteristics of EPOCH participants who have genotyping data and at least one outcome measurement

	rs10305420			rs6923761			rs1042044		
	CT or TT	CC	p	GA or AA	GG	p	CA or AA	CC	p
N	203	156		167	192		249	110	
Female	132 (51%)	100 (49%)	0.78	95 (44%)	137 (55%)	0.016	164 (53%)	68 (45%)	0.11
GDM	39 (15%)	47 (23%)	0.024	44 (20%)	42 (17%)	0.34	54 (17%)	32 (21%)	0.33
Race/ethnicity*			<0.0001			<0.0001			0.029
White	158 (61%)	93 (46%)		140 (65%)	111 (45%)		180 (58%)	71 (47%)	
Hispanic	87 (33%)	74 (37%)		66 (31%)	95 (38%)		95 (31%)	66 (43%)	
Black	6 (2%)	25 (12%)		5 (2%)	26 (11%)		20 (6%)	11 (7%)	
Other	10 (4%)	11 (5%)		5 (2%)	16 (6%)		17 (5%)	4 (3%)	
Age at visit 1	10.3 (1.4)	10.3 (1.6)	0.91	10.4 (1.4)	10.3 (1.6)	0.53	10.2 (1.4)	10.4 (1.5)	0.094
Age at visit 2	16.6 (1.2)	16.7 (1.2)	0.66	16.7 (1.2)	16.7 (1.2)	0.94	16.7 (1.2)	16.6 (1.2)	0.72

Continuous variables are presented as mean and SD, with comparisons test using the *t* test. Categorical variables are presented as number and percent. Unless otherwise noted, comparisons of categorical variables were conducted using the χ^2 test. *Because of small cell sizes, group comparisons of race/ethnicity were conducted using the Fisher exact test.

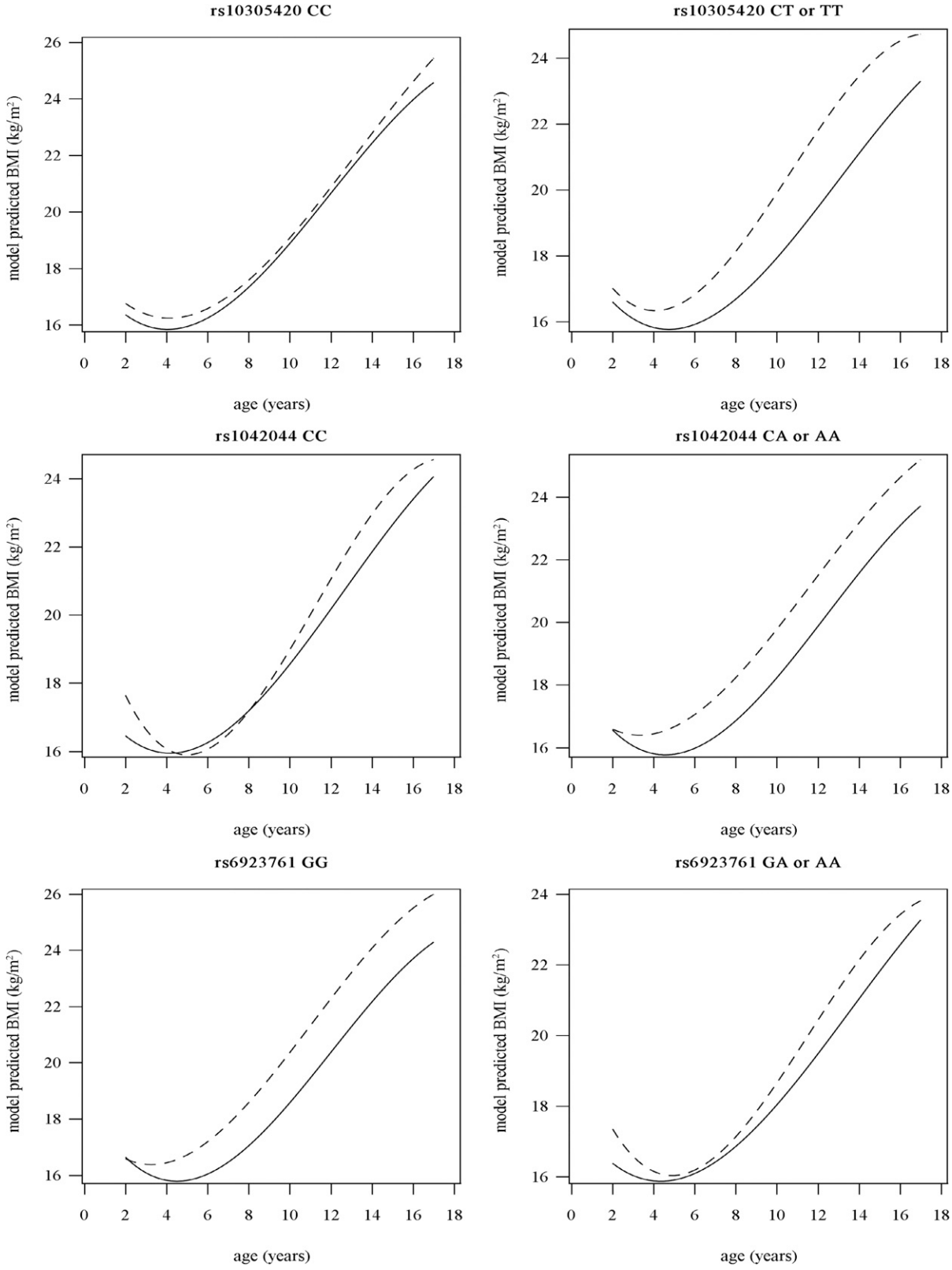

Figure 2—*GLP-1R* polymorphisms significantly modify the association between GDM and BMI growth across childhood and adolescence. The dashed line represents participants with GDM exposure. The solid line represents participants with no GDM exposure.

BMI of 1.71 kg/m^2 (95% CI: 0.20, 3.21) when compared with the minor allele group with GDM exposure, with BMI of 1.79 kg/m^2 (95% CI: 0.61, 2.96), when compared with major allele homozygotes without GDM exposure, and a BMI of 2.33 kg/m^2 (95% CI: 1.13, 3.52) when compared with the minor allele group without GDM exposure.

Table 2—Interactions between *GLP-1R* polymorphisms and exposure to maternal GDM on surrogate markers of glucose-insulin homeostasis

	rs10305420		rs6923761		rs1042044	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Glucose, baseline	6.10 (−4.30, 16.51)	0.25	9.03 (−1.15, 19.22)	0.082	−6.52 (−17.04, 3.99)	0.22
HOMA2-IR	−0.02 (−0.29, 0.26)	0.89	0.14 (−0.13, 0.41)	0.32	−0.01 (−0.29, 0.27)	0.96
HOMA2-β	−0.04 (−0.23, 0.15)	0.68	0.03 (−0.16, 0.22)	0.75	0.04 (−0.15, 0.24)	0.66
Insulinogenic index	−0.31 (−2.64, 2.02)	0.79	0.81 (−1.48, 3.10)	0.49	−0.75 (−3.11, 1.61)	0.53
Oral disposition index	−0.56 (−5.51, 4.38)	0.82	−1.87 (−6.71, 2.97)	0.45	0.01 (−5.01, 5.03)	>0.99

Surrogate Markers of Glucose-Insulin Homeostasis

rs6923761 did not significantly modify associations of GDM with glucose or insulin levels across OGTT or with surrogate markers for glucose-insulin homeostasis (all interaction *P* values >0.05) (Table 2).

rs1042044

BMI Growth

As shown in Supplementary Table 3, rs1042044 modified the association between GDM and BMI growth across childhood and adolescence, including the trajectory of BMI growth ($P = 0.0002$) and the velocity of BMI growth ($P = 0.0002$). More about the velocity analysis, including estimates of direction and magnitude, appears in Supplementary Results 1. Relationships are shown visually in Fig. 2. Exposure to GDM was associated with higher average BMI. However, this association was most pronounced among individuals with the minor allele for rs1042044 (i.e., genotypes CA or AA). These individuals had significant differences in average BMI by GDM exposure from the ages of 4 to 14 years (all $P < 0.05$). As an example, the average BMI at age 10 years was 1.55 kg/m^2 (95% CI: 0.50, 2.60) higher among participants with the minor allele with GDM exposure when compared with those without GDM exposure. Among major allele homozygotes for rs1042044 (i.e., genotype CC), there were no significant differences in average BMI by GDM exposure across childhood or adolescence.

Surrogate Markers for Glucose-Insulin Homeostasis

rs1042044 did not significantly modify any of the associations of GDM with glucose or insulin levels across OGTT or with surrogate markers for glucose-insulin homeostasis (all interaction *P* values >0.05) (Table 2).

CONCLUSIONS

Summary of Main Findings

Consistent with our first hypothesis, we found that common *GLP-1R* polymorphisms, GDM exposure, and their interaction were associated with BMI growth across childhood and adolescence in a diverse cohort of youth from Colorado. As expected, participants exposed to maternal GDM in utero had the highest average BMI across time. However, the detrimental effect of GDM exposure was further exacerbated among youth with rs10305420 genotype CT or TT, rs6923761 genotype GG, and rs1042044 genotype CA or AA. In contrast to our second hypothesis, the interaction between *GLP-1R* polymorphisms and GDM exposure was not associated with markers of glucose-insulin homeostasis.

GLP-1R Polymorphisms, GDM Exposure, and BMI Growth

For rs10305420 and rs1042044, participants with the minor allele appeared to be more vulnerable to GDM exposure than participants who were homozygous for the major allele. The minor allele group with GDM exposure had the fastest BMI growth velocity during early childhood, with significant differences in average BMI during middle childhood and adolescence, when compared with the minor allele group without GDM exposure. There were no differences in average BMI by GDM exposure for participants who were homozygous for the major allele. For rs6923761, major allele homozygotes appeared to be more vulnerable to GDM exposure than participants with the minor allele. Major allele homozygotes who were exposed to GDM had faster BMI growth velocity during childhood and significantly higher average BMI than all other participants in the cohort.

These findings are an important contribution to the literature, because they provide the first evidence of interaction between *GLP-1R* polymorphisms and GDM on BMI growth during childhood and adolescence. Previously, researchers, including us (15), have studied the relationship of GDM (4,6,7) and *GLP-1R* polymorphisms on BMI growth during childhood and adolescence independently. Many studies, including the EPOCH study (6,7), have shown that GDM exposure is associated with higher BMI and faster BMI growth across childhood and adolescence. Evidence of an interaction between *GLP-1R* polymorphisms and GDM on BMI growth can help to delineate the highest risk subgroups for preventative action.

The association between rs6923761 and anthropometrics has been studied extensively among adults. Among adult populations in Spain, de Luis et al. (25,29) reported that major allele homozygotes had higher BMI, weight, waist circumference, and insulin resistance compared with the minor allele group. This aligns with our previous findings regarding children (15). A study from the UK Biobank showed that adults with the minor allele for rs1042044 had lower BMI (23). In our study among youth, participants with the minor allele without GDM exposure had the lowest BMI growth, although not statistically different from major allele homozygotes without GDM exposure.

Gene by environment studies assist with refining our understanding of why GDM exposure increases BMI growth among some, but not all, children. Several studies have failed to show a positive association between GDM exposure and childhood BMI (11–13), highlighting that GDM may not be a sufficient cause for elevated BMI growth among all children. Indeed, we found that *GLP-1R* polymorphisms explain some of the heterogeneity in the relationship between GDM exposure and BMI growth.

It is possible that the *GLP-1R* polymorphisms reported here are not causally associated with BMI growth. Instead, we may be capturing associations with a different, true, causal variant that is tagged by the *GLP-1R* polymorphisms through linkage disequilibrium. Understanding causal effects would require additional biological studies, including mechanistic studies of potential action across multiple human tissues from the pancreas to the brain. These mechanistic studies would also permit examination of mediators or moderators of the causal gene's effects on BMI trajectories, including, potentially, weight gain velocity in the first year of life, breastfeeding or formula feeding, early nutrition, sugar-sweetened beverages intake, diet, sedentary behavior, low physical activity, screen time, or stress, for example.

GLP-1R Polymorphisms, GDM Exposure, and Glucose-Insulin Homeostasis

The relationship between GDM and BMI has been explored extensively (6,7). Exposure to hyperglycemia in utero promotes fetal overexpression of insulin (30). Insulin acts as a growth factor, increasing fetal growth and leading to increased birth weight, with higher BMI, obesity, and risk for type 2 diabetes in the offspring (4,13,31–37). The GLP-1 receptor also plays a direct role in insulin secretion, signaling Ca^{2+} mobilization, cAMP accumulation, and phosphorylation of extracellular signal-related kinase 1/2 (22). GLP-1R gene variation may affect the structure and function of the receptor, modifying β-cell efficiency and insulin secretion.

In this analysis, we did not observe a joint effect of GDM and *GLP-1R* polymorphisms on surrogate markers of insulin secretion or β-cell function. We had expected to see a joint effect, given that prior studies in this cohort found that GDM exposure (8) and *GLP-1R* polymorphisms (15) rs10305420 and rs6923761 were each independently associated with lower estimated insulin sensitivity. This could suggest that GDM exposure and polymorphisms of the GLP-1R gene act through different pathways to influence BMI growth and glucose-insulin homeostasis.

Strengths and Limitations

This study has both strengths and limitations. The EPOCH study was conducted among a diverse population of children, with data collected longitudinally from birth through adolescence. The study oversampled on GDM exposure to increase power for association studies between GDM exposure and offspring health outcomes. Repeated measurements of height and weight throughout the life course allowed for refined modeling of trajectories of BMI growth, which are more informative than single assessments of BMI. There were also several limitations. Since participant samples were not directly genotyped for *GLP-1R* polymorphism rs10305420, we imputed the genotype for this study. While the genotype imputation score for rs10305420 was >95%, direct genotyping could reduce measurement bias. Additionally, our sample size for this study was relatively small (n = 464) for testing two- and three-way interactions among single measurements from adolescent OGTT, which is inherently variable. It is possible that nonsignificant findings for surrogate markers of glucose-insulin homeostasis were due to limited power, lack of association, or both. Thus, the results need to be replicated in larger cohorts. We used surrogate measures of insulin sensitivity, insulin secretion, and β-cell function. While these measures correlate well with gold standard clamp-based measurements (38,39), more direct and detailed measures of such traits, such as those derived from minimal modeling of OGTTs with multiple sampling time points, are required to fully understand the physiological effects of GDM exposure and *GLP-1R* polymorphisms on glucose-insulin homeostasis. Finally, models of OGTT outcomes accounted for sex and age, rather than pubertal staging, as the EPOCH study only collected self-reported Tanner stage, which is not well-accepted as a reliable metric of pubertal stage (40).

Common *GLP-1R* polymorphisms modified the relationship between GDM exposure and BMI growth across childhood and adolescence. Both exposure to maternal GDM and *GLP-1R* polymorphisms were independently associated with BMI growth across childhood and adolescence, with joint exposure leading to a further increase in BMI growth. While GDM is a known risk factor, *GLP-1R* polymorphisms may spotlight children who are at the highest risk for rapid BMI growth and assist clinicians with defining populations at need for intervention. There were no joint effects on surrogate markers of glucose-insulin homeostasis, suggesting, perhaps, that GDM exposure and *GLP-1R* polymorphisms may act through different mechanisms. This study is among the first to characterize joint associations between *GLP-1R* polymorphisms and GDM exposure. Consequently, further studies are needed to replicate these results, and to explore the pathways underlying the joint relationships.

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Author Contributions. All authors critically reviewed and edited the manuscript, and provided final approval of the version to be published. K.K.H. led the conception and design of the study, and the analysis and interpretation, and wrote the original draft of the manuscript. D.H.G. assisted with the conception and design of the study, and provided mentorship for statistical analysis and data interpretation. L.A.L. provided mentorship on study design and for statistical analysis and data interpretation. E.M.L. assisted with the data analysis. L.A.V. assisted with statistical analysis and data interpretation. I.R.K. assisted with data interpretation. M.G.C. provided mentorship on study design and data interpretation. W.P. provided mentorship on study design and data interpretation. D.D. supervised the conception and design of the study, analysis, and data interpretation. D.D. also served as the principal investigator for the EPOCH study. K.K.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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