Associations of prenatal exposure to impaired glucose tolerance with eating in the absence of hunger in early adolescence

Ivonne P.M. Derks, Marie-France Hivert, Sheryl L. Rifas-Shiman, Véronique Gingras, Jessica G. Young, Pauline W. Jansen, Emily Oken.

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ABSTRACT

Objective: Exposure to impaired gestational glucose tolerance has been shown to have sex-specific associations with offspring obesity risk, perhaps by affecting the development of appetite regulation. We examined the extent to which prenatal exposure to impaired glucose tolerance was associated with eating in the absence of hunger (EAH) in early adolescent offspring, and in turn, whether EAH was cross-sectionally associated with body composition.

Methods: We included data from 1097 adolescents participating in Project Viva, a pre-birth longitudinal cohort. We obtained results of 2-stage prenatal glycemic screening (50g glucose challenge test, followed if abnormal by 100g oral glucose tolerance test) at 26-28 weeks gestation, and categorized mothers as having normal glucose tolerance, isolated hyperglycemia (IH, n=92, 8.4%), impaired glucose tolerance (IGT, n=36, 3.3%), or gestational diabetes mellitus (GDM, n=52, 4.7%). At a median age of 13 years, offspring reported on two modified items of the Eating in the Absence of Hunger in Children and Adolescents questionnaire, we measured height and weight, and performed dual X-ray absorptiometry scans to assess fat- and fat free mass. We used multivariable linear regression analyses adjusted for sociodemographic and prenatal covariates, including maternal pre-pregnancy BMI.

Results: On a 10-point scale, mean (SD) EAH score was 4.4 points (SD=1.5) in boys and 4.4 (SD=1.4) in girls. In girls, prenatal exposure to both IH and IGT was associated with more EAH compared with normal glucose tolerance (e.g. for IH: 0.56 points, 95%CI: 0.17, 0.96), whereas in boys, prenatal exposure to IGT was associated with less EAH (−0.81 points, 95%CI: −1.41, −0.21). We did not observe an association between exposure to GDM and EAH, nor did we observe associations between EAH and body composition in early adolescence.

Conclusions: These findings suggest sex-specific associations of exposure to impaired gestational glucose tolerance with offspring EAH in early adolescence.

INTRODUCTION

In the United States (US), the prevalence of maternal gestational diabetes mellitus (GDM) increased during the past 20 years and ranged between 5.8% and 9.2% of all pregnancies in 2010.[1-3] Longitudinal studies demonstrate that offspring exposed to impaired gestational glucose tolerance (defined as all abnormal prenatal glucose tolerance screening outcomes, ranging from isolated hyperglycemia to GDM) have an increased risk of obesity and impaired glucose tolerance during childhood and adolescence.[4-9] A possible mechanism by which impaired gestational glucose tolerance could affect body composition in childhood and adolescence is via appetite regulation.

Exposure to impaired gestational glucose tolerance might affect the intrauterine programming of appetite regulation. Neuroendocrine feedback systems between the gut, brain and adipose tissue regulate appetite. Balanced levels of insulin, leptin and ghrelin signal the hypothalamus to maintain energy homeostasis, but resistance to these hormones disturbs satiety signaling and may lead to increased food intake in response to external food cues rather than hunger.[10,11] Disturbances in this mechanism in offspring caused by maternal diet, parental obesity and GDM have been previously reported in animal studies.[12-16] Resistance to satiety signaling in the hypothalamus might also result in an increase in food intake in humans. Fisher and Birch conceptualized "eating in the absence of hunger (EAH)" in 1999, which can be described as eating past satiety in response to external food cues and indicating disinhibition in eating.[17] A recent systematic review including cross-sectional and prospective studies showed that children or adolescents with a higher weight status often showed more EAH, and results were often sex-specific.[18]

Parental obesity has also been associated with more EAH in the offspring. Francis et al.[19] showed that having overweight parents was associated with more EAH in girls, whereas Faith et al.[20] showed that high maternal pre-pregnancy BMI was associated with more EAH in boys. Furthermore, children from obese parents have been found to have a higher preference for high-fat food and a tendency towards overeating.[21] We are aware of only one study that examined the association between exposure to maternal gestational glucose tolerance and offspring EAH. Shapiro et al.[22] showed among 268 US adolescents that GDM exposure *in utero* was associated with more EAH in females, but not in males. In turn, more EAH was associated with a higher overall energy intake, but whether GDM exposure was associated with energy intake or adiposity was not examined. Thus, more studies are needed to examine whether offspring exposed to impaired gestational glucose tolerance show more EAH.

The aim of this study was to examine the extent to which prenatal exposure to impaired gestational glucose tolerance is associated with EAH in early adolescent offspring. Early adolescence may be a sensitive period for the development of eating problems as EAH appears to peak during this life stage.[23] Additionally, we examined the extent to which exposure to impaired gestational glucose tolerance was associated with self-reported sugar-sweetened beverage (SSB) intake and consumption of energy-dense, low nutritive foods as indicators of diet quality. Lastly, we examined the cross-sectional relationship between EAH and body composition in early adolescence.

METHODS

Study population

This study was embedded in Project Viva, a prospective pre-birth cohort situated in Eastern Massachusetts, US. Between April 1999 and July 2002, pregnant women were recruited at their initial prenatal visit from Atrius Harvard Vanguard Medical Associates. Informed consent was given by all mothers, and the Institutional Review Boards of participating institutions approved the study. All procedures were in accordance with the ethical standards established by the declaration of Helsinki.[24] All Project Viva questionnaires are available at https://www.hms.harvard.edu/viva/data-collection-by-visit.html.

In total, 2128 mothers had a live singleton birth in Project Viva. We excluded 16 mothers with a previous diagnosis of type 1 or type 2 diabetes and 45 mothers without prenatal glycemic screening data. From the remaining 2067 mothers, 1161 adolescents had any early teen data available. We excluded 64 adolescents with missing EAH data, resulting in a final study sample of 1097 mother-child pairs for analysis. We measured height and weight in 1000 of these adolescents, and of those, 715 adolescents had body composition measures.

Compared to excluded participants (n=1031), mothers of the 1097 included adolescents were older at enrollment (32.3 years vs. 31.3 years), were more likely to be white (66.2% vs. 60.8%) and had a higher annual household income (>$70,000 per year, 61.8% vs. 53.5%). Mothers of included vs. excluded participants had similar mean maternal pre-pregnancy BMI (24.7 vs. 25.1 kg/m^2) and gestational weight gain before glycemic screening (9.2 kg vs. 9.3 kg).

Procedures

At the age of 13 years, Project Viva staff invited adolescents to participate in the early teen wave. At an in-person visit, or via mail or online, adolescents completed the early teen questionnaire, including the assessment of EAH, SSB intake and consumption of energy-dense, low nutritive foods. During the early teen visit, trained research assistants collected objective physical health measures.

Measures

Maternal gestational glucose tolerance

Obstetric clinicians assessed maternal gestational glucose tolerance status by routine 2-stage prenatal glycemic screening at 26-28 weeks of pregnancy. All mothers completed a non-fasting 50g oral Glucose Challenge Test (GCT). If serum blood glucose exceeded 140 mg/dL after one hour, mothers were referred for a fasting three-hour 100g Oral Glucose Tolerance test (OGTT). OGTT results were considered abnormal when blood glucose was >95 mg/dL at baseline, >180 mg/dL after one hour, >155 mg/dL after two hours or >140 mg/dL after three hours. Mothers were diagnosed with GDM if they had two or more abnormal values on the OGTT. We categorized mothers with one abnormal result on the OGTT as having Impaired Glucose Tolerance (IGT), and mothers with an abnormal GCT but normal OGTT as having isolated hyperglycemia (IH). Clinicians typically instructed mothers diagnosed with GDM to check their fasting blood glucose levels daily, arranged follow-up with a nutritionist, provided advice about management with diet and physical activity, or prescribed insulin.[25] In our sample, 10 mothers with GDM and 1 mother with IGT were treated with insulin. In general, clinicians managed mothers with IGT or IH similar to normal glycemic mothers and therefore they typically did not receive further screening or treatment. As secondary exposures, we considered other indicators of maternal glycemic status during pregnancy including the serum blood glucose levels in mg/dL from the GCT, and fructosamine levels (μmol/l) measured in blood collected in the second trimester of pregnancy, reflecting mean blood sugar levels over the past 2-3 weeks. We transformed glucose and fructosamine levels into z-scores for comparison purposes.

Eating in the absence of hunger

We assessed self-reported EAH using two modified items derived from the Eating in the Absence of Hunger in Children and Adolescence questionnaire (EAH-C).[26] The questions were: 1. "Imagine you are eating a meal or snack at home or in a restaurant. Imagine that you have eaten enough so you are not hungry anymore. How often would you keep eating?" and 2. "Imagine you ate a meal or snack a little while ago and are not hungry anymore. How often would you start eating again?" Response options were on a five-point scale ranging from 1- never to 5- always. Internal consistency between both items was considered acceptable, with a Cronbach's α of 0.67. Only when adolescents completed both items, we calculated sum scores (ranging from 2 to 10 points).

Sugar Sweetened Beverage intake

Adolescents reported on beverage intake with 10 questions about intake of soda, diet soda, sports drinks, low-calorie sports drinks, energy drinks, juice, fruit and flavored drinks, milk, flavored milk, and water. Five response options ranged from less than once per week to twice or more per day. We combined questions on sugary soda, sport- and energy drinks, fruit- and flavored drinks and flavored milk to generate an estimate of total daily intake of SSB in servings per day.

Consumption of energy-dense, low nutritive foods

Adolescents reported on two items taken from PrimeScreen, a validated semi-quantitative food frequency questionnaire:[27] 1. How often have you eaten baked products (such as donuts, cookies, muffins, crackers, pastries, cakes or sweet rolls) during the past month? and 2. How often have you eaten deep-fried foods (such as deep-fried chicken, fish or seafood, French fries, onion rings) during the past month? Five response options ranged from less than once per week to twice or more per day. We added both questions to generate an estimate of total consumption of energy-dense, low nutritive foods in servings per day.

BMI and body composition

Trained research assistants measured adolescent's height and weight without shoes and heavy clothing. We calculated BMI in kg/m^2 and determined sex and age specific BMI z-scores from US national reference data.[28] Further, whole-body DXA scans (Hologic model Discovery A, Hologic, Bedford, MA) were conducted, using Hologic software version 12.6 for scan analysis. Scans were checked for positioning, movement and artifacts. We calculated fat mass index (FMI) as total fat mass (kg)/ height $(m)^2$, fat free mass index (FFMI) as total fat free mass (kg)/ height $(m)^2$ and percentage body fat as total fat mass (kg)/ total weight (kg).

Covariates

Based on previous literature and theory,[8,18] we considered several possible confounders. During the first prenatal visit, mothers reported on their age, educational level, marital status, household income and parity, pre-pregnancy- and paternal weight and height. In the first trimester, mothers completed a validated semi-quantitative Food Frequency Questionnaire (FFQ) adapted for pregnancy, from which we calculated western and prudent dietary pattern scores using principal components analysis (PCA).[29-31] We obtained serial prenatal weights from medical records and calculated gestational weight gain only up to 26 weeks of gestation since subsequent weight gain can be influenced by diagnosis and treatment of GDM. We obtained child sex, birthweight and birth date from medical records and calculated sex-specific birthweight for gestational age z-scores using US reference data.[32] In early childhood, mothers reported on their child's race/ethnicity.

Statistical analyses

We calculated means and frequencies of each covariate according to maternal gestational glucose tolerance status. We included covariates in the main analyses when they were associated with EAH, SSB intake, or consumption of energy-dense, low-nutritive foods, by bivariate analyses. In general, we did not include intermediate covariates in our models in order to prevent collider bias (for instance, the association between impaired gestational glucose tolerance and EAH was not adjusted for birthweight, and was only adjusted for gestational weight gain until the time of GDM screening but not later weight gain).[33]

We used multivariable linear regression analyses to examine associations of impaired gestational glucose tolerance with EAH sum scores. Three models are presented: the basic model, adjusted for child sex and age. Model 2 was additionally adjusted for pre-pregnancy and prenatal covariates (maternal age, education, marital status, parity, pre-pregnancy BMI, gestational weight gain, and prudent diet and western diet scores during pregnancy; household income and paternal BMI; and child race/ethnicity). Model 3 was additionally adjusted for child BMI z-score in early adolescence, as this could be a proxy for unmeasured confounders. We repeated these analyses with the outcomes of SSB intake and consumption of energy-dense, low-nutritive foods, and BMI z-score in early adolescence (model 2 only).

Next, we studied cross-sectional associations of EAH with body composition using multivariable linear regression analyses. Two models were created: the basic model, adjusted for sex and age; second, additionally adjusted for maternal age, education, marital status, parity, pre-pregnancy BMI, gestational weight gain, prudent diet and western diet scores during pregnancy; household income and paternal BMI; and child race/ethnicity and birth weight for gestational age z-score.

In sensitivity analyses, we repeated our analyses of maternal gestational glucose tolerance with EAH excluding those mothers who were treated with insulin during pregnancy. We also studied associations of child BMI z-score with adolescent EAH, again using multiple linear regression analyses. We calculated the change in BMI (Δ BMI) from the mid-childhood to the early teen visit.

We tested interactions with sex in confounder-adjusted models, given previous studies showing sex differences in child anthropometrics by impaired gestational glucose tolerance within Project Viva,[8] as well as sex-specific findings in previous literature.[18,22] We presented stratified analyses when a significant interaction effect ($p<0.05$) by sex was found.

We checked diagnostics for linear regression analyses and confirmed concordance with model assumptions. Multiple imputation was used to estimate missing data on covariates. All study variables were included in the imputation model and results are based on pooled results of 50 imputed datasets. Multiple imputation was performed with SAS version 9.4 (Cary, NC) and analyses in SPSS version 24.0 (IBM corp.).

RESULTS

Sample characteristics according to maternal gestational glucose tolerance status are provided in Table 3.1. Of the 1097 adolescents, 917 (83.6%) were prenatally exposed to normal glucose tolerance, 92 to IH (8.4%), 36 to IGT (3.3%), and 52 to GDM (4.7%). Adolescents exposed to IGT reported slightly lower scores of EAH (mean=4.2 points, SD=1.6), while adolescents exposed to IH or GDM reported slightly higher scores of EAH (IH, mean= 4.6 points, SD=1.4 or GDM, mean= 4.6 points, SD=1.4) compared to normal glucose tolerance (mean= 4.4, SD= 1.4). Mothers with GDM had a higher pre-pregnancy BMI but lower early pregnancy gestational weight gain, compared to normal glycemic mothers. Adolescents prenatally exposed to impaired gestational glucose tolerance were less often white and had a higher fat mass in early adolescence.

Table 3.1. Characteristics of 1097 adolescents in Project Viva according to maternal gestational glucose tolerance status

	Overall n=1097	**Maternal gestational glucose tolerance status**			
		Normal n=917	**IH n=92**	**IGT n=36**	**GDM n=52**
Prenatal characteristics					
Maternal educational level, n (%)					
< College graduate	307 (28)	254 (28)	19 (21)	12 (33)	22 (42)
≥ College graduate	790 (72)	663 (72)	73 (79)	24 (67)	30 (58)
Mother married or cohabitating, n (%)					
No	81 (7)	70 (8)	4 (4)	4 (11)	3 (6)
Yes	1016 (93)	847 (92)	88 (96)	32 (89)	49 (94)
Annual household income, n (%)					
≤ $ 70 000	419 (38)	348 (38)	33 (36)	14 (38)	25 (48)
> $ 70 000	678 (62)	569 (62)	59 (64)	22 (62)	27 (52)
Nulliparous, n (%)					
No	563 (51)	470 (51)	48 (52)	21 (58)	24 (46)
Yes	534 (49)	447 (49)	44 (48)	15 (42)	28 (54)
Maternal age at enrollment, years	32.3 (5.0)	32.0 (5.1)	34.0 (4.3)	33.4 (3.9)	32.9 (3.8)
Maternal pre-pregnancy BMI, kg/m^2	24.7 (5.1)	24.4 (5.0)	25.2 (5.0)	25.4 (4.2)	28.1 (6.4)
Gestational weight gain up to 26 weeks gestation, kg	9.2 (3.8)	9.3 (3.7)	8.7 (3.7)	10.0 (4.1)	8.3 (4.8)
Maternal prudent dietary pattern 1st trimester z-score	0.01 (0.99)	−0.00 (0.99)	0.09 (0.94)	−0.10 (0.85)	0.14 (1.07)
Maternal western dietary pattern 1st trimester z-score	−0.03 (0.95)	−0.04 (0.96)	−0.04 (0.87)	−0.19 (0.89)	0.22 (1.02)
Paternal BMI, kg/m^2	26.4 (4.0)	26.3 (4.0)	27.2 (4.2)	26.2 (2.9)	26.7 (3.6)

Table 3.1. Characteristics of 1097 adolescents in Project Viva according to maternal gestational glucose tolerance status (*continued*)

	Overall n=1097	**Maternal gestational glucose tolerance status**			
		Normal n=917	**IH n=92**	**IGT n=36**	**GDM n=52**
Child characteristics					
Sex, n (%)					
Boys	552 (50)	459 (50)	40 (43)	25 (69)	28 (54)
Girls	545 (50)	458 (50)	52 (57)	11 (31)	24 (46)
Race/ethnicity, n (%)					
Black	160 (15)	135 (15)	9 (10)	6 (17)	10 (19)
Hispanic	49 (4)	39 (4)	6 (7)	1 (3)	3 (6)
Asian	35 (3)	29 (3)	2 (2)	2 (6)	2 (4)
White	726 (66)	605 (66)	68 (74)	22 (61)	31 (60)
Other	126 (11)	108 (12)	7 (8)	5 (14)	6 (12)
Gestational age at birth, weeks	39.6 (1.6)	39.6 (1.6)	39.9 (1.1)	39.9 (1.0)	38.9 (1.7)
Birth weight, kg	3.49 (0.53)	3.47 (0.54)	3.62 (0.47)	3.75 (0.45)	3.52 (0.49)
Birth weight for gestational age z-score	0.19 (0.95)	0.14 (0.95)	0.37 (0.94)	0.55 (0.90)	0.35 (0.88)
Early adolescence					
Age at visit, years	13.3 (1.0)	13.3 (1.0)	13.1 (0.8)	13.2 (0.9)	13.5 (1.0)
BMI z-score	0.36 (1.06)	0.33 (1.07)	0.53 (1.05)	0.34 (0.95)	0.70 (0.92)
BMI category, n (%)					
Normal weight (<85th percentile)	731 (73)	625 (75)	50 (58)	25 (81)	31 (65)
Overweight (85th-<95th percentile)	148 (15)	114 (14)	23 (27)	2 (6)	9 (19)
Obese (≥85th percentile)	121 (12)	96 (11)	13 (15)	4 (13)	8 (17)
Fat Mass Index, kg/m^2	6.3 (3.1)	6.2 (3.0)	6.9 (2.9)	6.3 (3.0)	7.4 (3.6)
Fat Free Mass Index, kg/m^2	14.9 (2.1)	14.9 (2.1)	14.7 (1.9)	14.5 (1.6)	15.9 (2.1)
% Body fat	28.5 (7.5)	28.1 (7.5)	30.9 (7.0)	29.0 (8.5)	30.2 (7.6)
Eating in the absence of hunger sum score[a]	4.4 (1.4)	4.4 (1.4)	4.6 (1.4)	4.2 (1.6)	4.6 (1.4)
Sugar sweetened beverages, servings/day	0.8 (0.9)	0.8 (0.9)	0.7 (0.9)	0.9 (0.8)	0.8 (0.8)
Energy-dense, low nutritive foods, servings/day	0.5 (0.4)	0.5 (0.4)	0.5 (0.3)	0.5 (0.4)	0.5 (0.4)

Values are means (SD) or frequencies (%). [a] Range: 2-10 points.

Table 3.2. Associations of maternal gestational glucose tolerance status with offspring eating in the absence of hunger in early adolescence among 1097 adolescents in Project Viva

	Prenatal exposure to glucose tolerance status	N	Frequency (%)/mean (SD)	Eating in the absence of hunger score in early adolescence		
				Model 1 Basic model β (95%CI)	Model 2 Confounder adjusted β (95%CI)	Model 3 BMI adjusted β (95%CI)
Boys	Maternal glucose tolerance status					
	Normal glycemic	459	83.2	*Reference*	*Reference*	*Reference*
	Isolated hyperglycemia	40	7.2	−0.22 (−0.70, 0.26)	−0.13 (−0.61, 0.35)	−0.14 (−0.62, 0.34)
	Impaired glucose tolerance	25	4.5	−0.77 (−1.37, −0.17)	−0.81 (−1.41, −0.21)	−0.79 (−1.39, −0.19)
	GDM	28	5.1	0.32 (−0.25, 0.89)	0.33 (−0.24, 0.91)	0.33 (−0.24, 0.90)
	Maternal serum glucose level after GCT, mg/dL	548	115.0 (27.9)	−0.06 (−0.18, 0.07)	−0.03 (−015, 0.10)	−0.03 (−0.15, 0.10)
	Second trimester fructosamine level, μmol/l	438	233.7 (49.6)	0.04 (−0.09, 0.17)	0.03 (−0.11, 0.16)	0.03 (−0.11, 0.16)
Girls	Maternal glucose tolerance status					
	Normal glycemic	458	84.0	*Reference*	*Reference*	*Reference*
	Isolated hyperglycemia	52	9.5	0.50 (0.12, 0.89)	0.56 (0.17, 0.96)	0.55 (0.16, 0.94)
	Impaired glucose tolerance	11	2.0	0.89 (0.08, 1.70)	0.76 (−0.05, 1.57)	0.75 (−0.06, 1.56)
	GDM	24	4.4	0.03 (−0.52, 0.59)	0.01 (−0.56, 0.57)	−0.01 (−0.58, 0.56)
	Maternal serum glucose level after GCT, mg/dL	545	111.6 (26.4)	0.10 (−0.02, 0.22)	0.12 (−0.01, 0.24)	0.12 (−0.01, 0.24)
	Second trimester fructosamine level, μmol/l	433	233.4 (45.5)	0.02 (−0.11, 0.16)	0.06 (−0.08, 0.19)	0.06 (−0.08, 0.19)

Maternal serum glucose level after GCT and first trimester fructosamine level are modeled as z-scores. Model 1 is adjusted for child age at outcome, Model 2 is additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; and child race/ethnicity. Model 3 is additionally adjusted for BMI z-score in early adolescence.

Sex differences were present in the association between IH and EAH and between IGT and EAH (both p<0.03, overall F(df1, df2) =4.78 (3, 1074), p= 0.003). Boys prenatally exposed to IGT reported less EAH compared to boys exposed to normal gestational glucose tolerance (model 2, confounder adjusted β=−0.81 points, 95%CI: −1.41, −0.21, Table 3.2 and Figure 3.1). No evidence of an association was found for EAH scores in boys exposed to other categories or for maternal glucose levels after the GCT and fructosamine levels. For girls, prenatal exposure to IH was associated with more EAH compared to exposure to normal gestational glucose tolerance (model 2, β= 0.56 points, 95%CI: 0.17, 0.96, Table 3.2 and Figure 3.1). Further, girls prenatally exposed to IGT also reported more EAH, (model 2, β= 0.76 points, 95%CI: −0.05, 1.57), although the confidence interval included zero. EAH scores were similar for GDM compared to normal glucose tolerance exposure. We further observed a positive association between maternal glucose levels after GCT with EAH in girls, but confidence intervals contained zero. For both sexes, additional adjustment for BMI z-score at 13 years did not attenuate the associations between im-

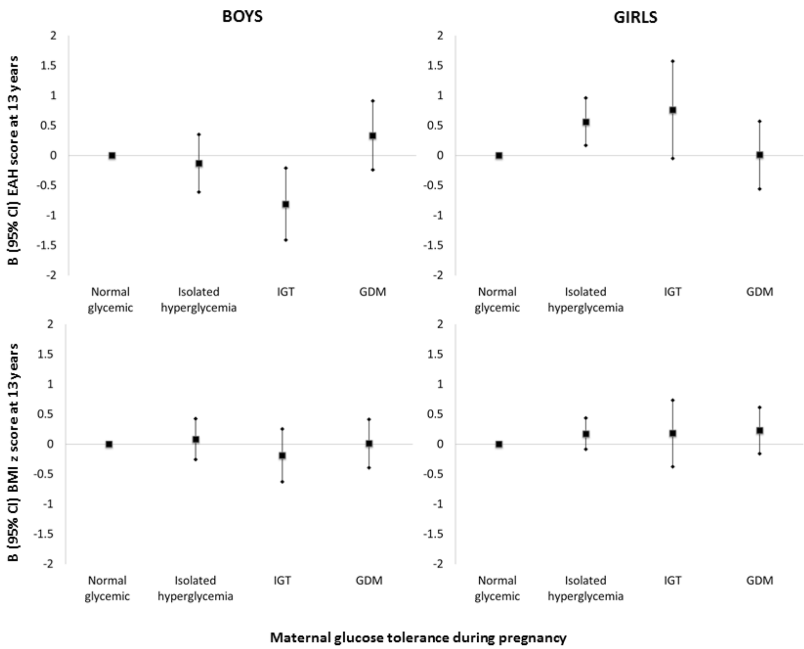

Figure 3.1. Adjusted linear regression coefficients and their associated 95% confidence intervals for eating in the absence of hunger (EAH) and BMI z-score in early adolescence (median age= 13 years), according to maternal glucose tolerance status during pregnancy and stratified by child sex (N=552 boys and N= 545 girls for EAH; N=496 boys and N=504 girls for BMI z-score). Effect estimates were adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; and child race/ethnicity and age at outcome assessment.

paired gestational glucose tolerance and EAH (Table 3.2, model 3). Figure 3.1 displays the associations between categories of gestational glucose tolerance and EAH scores as given in Table 3.2 (model 2), as well as associations between categories of gestational glucose tolerance with BMI z-score in early adolescence. Although patterns of associations of maternal glucose tolerance with BMI z-score were comparable to findings with EAH, no evidence for an association was found for BMI z-score in boys or girls prenatally exposed to impaired glucose tolerance (e.g. for IGT in girls: β= 0.18, 95%CI= −0.38, 0.73).

In Table 3.3 we show associations of exposure to impaired gestational glucose tolerance with SSB intake and consumption of energy-dense, low-nutritive foods. We observed a sex-interaction between exposure to GDM for SSB intake (p=0.03), overall F(df1, df2)= 1.70 (3, 1074), p=0.17. In boys, prenatal exposure to GDM was associated with less SSB intake (β= −0.29 servings/day, 95%CI: −0.65, 0.06), whereas in girls, exposure to GDM was associated with more SSB intake (β= 0.18 servings/day, 95%CI: −0.13,

Table 3.3. Associations of maternal prenatal gestational glucose tolerance status with offspring self-reported SSB intake and consumption of energy-dense, low nutritive foods in early adolescence

		SSB intake in early adolescence (servings/day)	Consumption of energy-dense, low nutritive foods in early adolescence (servings/day)
	Prenatal exposure to glucose tolerance status	**β (95% CI)**	**β (95% CI)**
Boys	Maternal glucose tolerance status		
	Normal glycemic	*Reference*	*Reference*
	Isolated hyperglycemia	−0.03 (−0.33, 0.27)	−0.09 (−0.24, 0.07)
	Impaired glucose tolerance	0.01 (−0.36, 0.37)	−0.08 (−0.27, 0.11)
	GDM	−0.29 (−0.65, 0.06)	0.03 (−0.16, 0.21)
	Maternal serum glucose level after GCT, mg/dL	−0.07 (−0.15, 0.00)	−0.02 (−0.06, 0.02)
	Second trimester fructosamine level, µmol/l	−0.02 (−0.11, 0.06)	0.02 (−0.02, 0.06)
Girls	Maternal glucose tolerance status		
	Normal glycemic	*Reference*	*Reference*
	Isolated hyperglycemia	−0.02 (−0.23, 0.19)	0.00 (−0.11, 0.11)
	Impaired glucose tolerance	0.18 (−0.27, 0.62)	0.22 (−0.01, 0.45)
	GDM	0.18 (−0.13, 0.49)	−0.04 (−0.20, 0.12)
	Maternal serum glucose level after GCT, mg/dL	0.02 (−0.05, 0.09)	0.01 (−0.03, 0.04)
	Second trimester fructosamine level, µmol/l	0.00 (−0.07, 0.07)	0.02 (−0.02, 0.06)

Serum glucose level after GCT and second trimester fructosamine level are modeled as z-scores. Effect estimates were adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity and age at outcome.

0.49), although confidence intervals contained zero. We did not observe a sex-interaction effect with consumption of energy-dense, low-nutritive foods (overall F(df1, df2)= 0.62 (3, 1066), p=0.60). Only in girls, exposure to IGT was associated with more consumption of energy-dense, low-nutritive foods (β= 0.22 servings/day, 95% CI: −0.01, 0.45), while no associations were observed in boys.

Cross-sectional associations between EAH and body composition are shown in Table 3.4. We did not observe a sex-interaction effect with EAH on body composition (e.g. BMI: F(df) =0.69 (980), p=0.41). Basic models showed that more EAH was positively associated with body composition measures (e.g. for FMI β= 0.20, 95% CI:0.05, 0.36) (model 1). All associations attenuated after additional adjustment for sociodemographic and prenatal factors (model 2). Maternal pre-pregnancy BMI, gestational weight gain and paternal BMI were important contributors to this attenuation of effect for all body composition outcomes.

Table 3.4. Cross-sectional associations between eating in the absence of hunger and body composition in early adolescence

Predictor		**Body composition**			
		BMI z-score β (95%CI)	**FMI β (95%CI)**	**FFMI β (95%CI)**	**% Body fat β (95%CI)**
Eating in the absence of	n	1000	715	715	715
hunger, per point	Model 1 Basic model	0.07 (0.03, 0.12)	0.20 (0.05, 0.36)	0.14 (0.03, 0.24)	0.37 (0.00, 0.75)
	Model 2 Confounder adjusted	0.04 (0.00, 0.08)	0.12 (−0.02, 0.26)	0.03 (−0.06, 0.12)	0.29 (−0.06, 0.64)

Model 1 was adjusted for sex and age at outcome. Model 2 was additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity, birth weight for gestational age z-score.

We found no associations between BMI z-score in mid-childhood and EAH in early adolescence, nor did we observe an association of BMI z-score change from mid childhood to early adolescence with EAH in early adolescence (Supplementary Table 3.1). Finally, we observed similar results after excluding mothers who were treated with insulin during pregnancy (not tabulated).

DISCUSSION

In this pre-birth cohort, we found sex-specific associations for prenatal exposure to impaired glucose tolerance with EAH in early adolescence. Girls prenatally exposed to IH or IGT reported more EAH, while boys exposed to IGT reported less EAH compared to adolescents exposed to normal glucose tolerance. Comparable sex-specific patterns of associations were found for impaired gestational glucose tolerance with BMI z-score, self-reported SSB intake and consumption of energy-dense, low nutritive foods in early adolescence, although the associations were weaker. We did not observe cross-sectional associations between EAH and body composition in early adolescence.

The observed sex differences in prenatal exposure to impaired glucose tolerance on EAH might reflect differential sensitivity to the intrauterine environment with a long-lasting effect on appetite regulation. Our finding that girls were especially sensitive to adverse effects from exposure to gestational glucose intolerance was consistent with the only previous study, to our knowledge, that examined the same relationship. Shapiro et al.[22] studied exposure to GDM versus no GDM and its association with EAH, whereas we extended this investigation by examining two intermediate categories of gestational glucose intolerance, namely IH and IGT. Remarkably, these two intermediate categories were associated with more EAH in girls, whereas exposure to GDM was not. This pattern may have resulted from treatment that mothers diagnosed with GDM received, while mothers with IH or IGT during pregnancy were generally treated the same way as mothers with normal glucose tolerance, thus presumably having higher levels of glycemia throughout the third trimester than normoglycemic women. The results were unchanged when we excluded women who received insulin treatment, although we had no information on degree of adherence to GDM treatment, suggesting that this pattern may still have resulted from treatment that mothers with GDM received, typically including glucose level monitoring, lifestyle changes and weight control. Although it can be assumed that mothers with GDM also received treatment in Shapiro et al., this was not reported. Our result that prenatal exposure to IGT was associated with less EAH in boys was partially in line with Shapiro et al., who reported a non-significant negative association in boys.[22]

An increasing number of studies have recently reported differential sensitivity to impaired gestational glucose tolerance by sex in relation to offspring health outcomes. Prior results in Project Viva showed that in female offspring, exposure to IGT during pregnancy had greater adiposity levels in mid-childhood, which is in line with our findings in girls. However, the same study showed that GDM exposure was associated with higher adiposity in boys, while we observed less EAH in boys exposed to GDM,[8] although relationships attenuated in early adolescence.[34] Other studies showed sex differential associations in growth and adiposity by maternal and cord blood C-peptide concentrations.[35,36] Moreover, Landon et al. showed that treatment of maternal hyperglycemia during pregnancy resulted in lower glucose levels in female offspring aged 5-10 only.[37] Our findings add to these studies by suggesting that sex differences *in utero* might also affect the development of long-term appetite regulation.

Prenatal exposure to impaired glucose tolerance might influence release of or sensitivity to leptin, resulting in more EAH in the offspring. A few studies reported higher (cord) blood leptin concentrations in offspring exposed to GDM,[38,39] or in boys exposed to IGT and GDM,[40] but also in girls of non-diabetic mothers compared to boys.[39] Furthermore, a Mendelian randomization study provided causal support for the premise that maternal hyperglycemia influences offspring leptin regulation.[41] Reduced leptin signaling in the hypothalamus might be a potential mechanism as this was shown in offspring of diabetic mothers in animal studies,[13] and fMRI studies in humans showed that the hypothalamus is connected with brain centers that process food reward.[42] Yet, whether prenatal exposure to impaired glucose tolerance affects long-term appetite regulation through disturbed leptin signaling in humans needs to be explored further.

The association between EAH and weight status has been extensively studied, and most cross-sectional studies showed that children with EAH have a higher weight status.[18] Most studies were, however, conducted during childhood, while studies suggest that EAH is increasing with age, with a peak in early adolescence.[23,43] Sex-specific associations have also been reported. In a series of prospective studies among 197 girls, EAH was associated with weight gain up to 13 years.[44-46] Two cross-sectional studies, however, examined associations in both sexes and only found associations for overweight boys.[47,48] Butte et al.[49] studied 879 children aged between 4-19 years old and found that EAH was not associated with weight gain over one-year follow-up, and similar findings were reported by Kelly et al.[50] We did not find an association with body composition in early adolescence after adjustment for confounders, nor did we find sex differences. These discrepancies in findings might be due to the lack of uniformity in the assessment of EAH and different settings where social desirability of limiting food intake might play a role, especially in girls.[18,48] Finally, our findings were in line with another study examining measures of adiposity other than BMI.[50] More studies are needed to examine whether EAH might prospectively influence adiposity levels later in adolescence.

Strengths and limitations

Strengths of this population-based study were its large sample size, the prospective data collection starting in the first trimester of pregnancy with several prenatal glycemic indicators, and DXA-derived body composition measures in addition to BMI. This study includes also some limitations. First, EAH was measured with two modified items of the EAH-C questionnaire. Usually, EAH is measured by observation in a lab setting,[17] but this is not always feasible in large cohorts. In treatment-seeking overweight children, total scores on EAH-C questionnaire were positively associated with total dietary intake.[51]

Yet, validity against observational EAH in a population-based cohort, including healthy weight children, has not been reported. Compared to the original items, only the stimulus for EAH was left out in our items. For instance: "How often do you keep eating because you are feeling depressed?" was changed into "How often do you keep eating?". Nevertheless, EAH was correlated with SSB intake (r = 0.22), but not with consumption of energy-dense low-nutritive foods in this sample (r = 0.09). Second, the sex-specific results might be a result of chance given small number of adolescents in each stratum. However, these sex-differential effects by gestational glucose tolerance were also previously reported for other outcomes in the present cohort, such as cord-blood hormone levels and child adiposity.[8,40] Loss to follow-up might have introduced selection bias and limits the generalizability, since included participants reported better socioeconomic conditions. The cross-sectional nature of associations between EAH and body composition limits causal interpretation even with adjustment for confounders. In all cases unmeasured confounding and measurement error may also bias our effect estimates.

Conclusions

These findings suggest sex-specific associations of exposure to impaired gestational glucose tolerance in offspring appetite regulation. Girls prenatally exposed to IH and IGT showed more EAH in early adolescence, whereas boys prenatally exposed to IGT showed less EAH. In early adolescence, EAH was not associated with body composition. These results suggest that impaired glucose tolerance might affect sex-specific intrauterine programming and long-term appetite dysregulation. More research is needed to further explain the early origins of sex differences in appetite regulation and how it affects adiposity later in life.

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SUPPLEMENT

Supplementary Table 3.1. Associations of change in child BMI z score from mid-childhood to early adolescence with eating in the absence of hunger in early adolescence

Child BMI measures		**Eating in the absence of hunger sum score in early adolescence β (95%CI)**
Mid childhood BMI z score	n	861
	Model 1	0.11 (0.01, 0.21)
	Model 2	0.06 (−0.05, 0.16)
Early adolescence BMI z score	n	1000
	Model 1	0.13 (0.05, 0.21)
	Model 2	0.09 (−0.01, 0.18)
Δ BMI z score	n	861
from mid childhood to early adolescence	Model 1	0.10 (−0.05, 0.26)
	Model 2	0.09 (−0.07, 0.24)

Model 1 was adjusted for sex and age at outcome. Model 2 was additionally adjusted for maternal age at enrollment, parity, educational level, marital status, pre-pregnancy BMI, gestational weight gain up to 26 weeks of gestation, and prudent and western dietary pattern scores; household income and paternal BMI; child race/ethnicity and birth weight for gestational age z-score.