Early Life and Obesity

Offspring risk of obesity in childhood, adolescence and adulthood in relation to gestational diabetes mellitus: a sex-specific association

Shanshan Li,[1,2] Yeyi Zhu,[1,3] Edwina Yeung,[1] Jorge E Chavarro,[2,4,5] Changzheng Yuan,[2,4,5] Alison E Field,[2,4,7,8] Stacey A Missmer,[2,4,6,7] James L Mills,[1] Frank B Hu[2,4,5] and Cuilin Zhang[1]*

[1]Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD, USA, [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA, [3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA, [4]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [5]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA, [6]Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [7]Division of Adolescent/Young Adult Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA and [8]Department of Epidemiology, Brown University, Providence, RI, USA

*Corresponding author. Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6710B Rockledge, Bethesda, MD 20817, USA. E-mail: zhangcu@mail.nih.gov

Abstract

Background: Animal data suggest sexually dimorphic programming of obesity in response to altered intrauterine environment, but the longitudinal impact of gestational diabetes mellitus (GDM) on sex-specific risk of offspring obesity in humans is unclear.

Methods: We conducted a prospective analysis of 15 009 US individuals (7946 female and 7063 male) from the Growing-Up Today Study, who were followed from 1996 (ages 9–14 years) through 2010. Height and weight from validated questionnaires were used to derive body mass index (BMI) at different ages. Obesity during childhood (< 18 years) and adulthood (≥ 18 years) were defined using the International Obesity Task Force and the World Health Organization criteria. GDM exposure was identified through self-reported questionnaires from mothers. Relative risks were estimated using multivariable log-binomial regression models with generalized estimating equations accounting for clustering within the same family.

Results: Male offspring born from pregnancies complicated by GDM had higher BMI compared with non-GDM offspring and had increased risk of obesity; the adjusted relative risk [RR, 95% confidence interval (CI)] was 1.47 (1.11–1.95) for all age groups,

1.59 (1.05–2.41) for late childhood, 1.48 (1.06–2.06) for adolescence and 1.39 (1.00–1.94) for early adulthood. No significant association between obesity and maternal GDM was observed among female participants (RR = 0.97, 95% CI: 0.71–1.33).

Conclusions: The association of GDM with offspring obesity from late childhood through early adulthood may differ by sex; a significant association was observed among male but not female offspring.

Key words: Diabetes, gestational, obesity, paediatric obesity

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Key Messages

- In this large prospective cohort of US women and their offspring with long-term follow-up, the adverse impact of GDM on offspring risk of obesity is sex-specific.
- Exposure to GDM *in utero* was significantly associated with increased risk of obesity among male participants only, and the elevated risk persisted across late childhood, adolescence and early adulthood.
- Girls born to women with GDM exhibited different patterns of obesity risk across early life stages compared with boys, with an increased but non-significant risk of obesity only at 18 years or above.

Introduction

Worldwide, approximately 155 million children aged 5 to 17 years are overweight or obese.[1] Once a child is obese, s/he is more likely to remain obese during adulthood. In 2014, approximately 1.9 billion adults were overweight and over 600 million were obese.[1] Therefore, it is important to identify risk factors that may contribute to the early prevention of obesity. Accumulating data suggest that exposure to hyperglycaemia *in utero*, as occurrs in gestational diabetes (GDM), may expose offspring to a lifelong increased risk of obesity.[2,3] As one of the most common pregnancy complications, GDM is complicating as much as 16.5% of pregnancies worldwide.[4,5] Increased intrauterine exposure to glucose, as exemplified among pregnancies complicated by GDM, may stimulate greater insulin secretion in the fetus, influence epigenetic modifications,[6] alter the developmental programming of appetite control, modulate the child's energy balance system and affect adipocyte metabolism.[3] These early life changes may subsequently lead to the development of obesity and adverse cardiometabolic health later in life.[2,3]

Although the association of GDM with offspring obesity has been investigated in a number of epidemiological studies,[7–9] findings are conflicting. This may be partly due to the fact that the association may vary by offspring age and become more evident later in life.[10] Nonetheless, studies on the long-term impact of GDM on obesity beyond infancy and childhood (i.e. in adolescence and early adulthood) remain sparse. In addition, emerging data from both animal and epidemiological studies suggest that there

is potential sex-specific sensitivity to the intrauterine environment in relation to the developmental programming of cardiometabolic outcomes, with males being more responsive to the intrauterine environment.[11,12] Thus, male offspring may be more vulnerable to the impaired maternal metabolic profile and suffer from more detrimental effects in the presence of a stressful event.[11] This sex dimorphism might lead to profound differential long-term health consequences. However, data on sex-specific associations of GDM with offspring obesity are very limited and mostly focused on the infancy and early childhood stages;[13–15] longitudinal, sufficiently powered studies beyond early childhood are warranted.

To address these critical knowledge gaps, in the present study we prospectively examined the sex-specific association between exposure to GDM *in utero* and subsequent long-term risk of obesity across late childhood, adolescence and early adulthood.

Methods

Study population

The Growing Up Today Study (GUTS) is an ongoing prospective cohort of 16 882 US participants recruited in childhood at ages 9 to 14 years.[16] Participants of the GUTS study are offspring of women in the Nurses' Health Study-II (NHS-II) which included ~120 000 female nurses aged 25–44 years at baseline in 1989.[17] Nurses reported their anthropometric and lifestyle information and medical history through a self-administered questionnaire every

2 years, such as body weight, pre-pregnancy weight, height, smoking status, parity, caesarean section, previous history of GDM, breastfeeding duration and geographical region. Participants in the GUTS study were followed from 1996 (mean age 12 years) through 2010 (mean age 25 years). These children' anthropometry, lifestyle and medical history information was collected annually between 1997 and 2001, and biennially between 2001 and 2010, such as body weight, height, smoking status, physical activity and menarche status. Dietary information was collected using semi-quantitative food frequency questionnaires annually over 1996–1999 and in 2001. The study was approved by the institutional review board of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

We excluded children with missing or with implausible values on baseline height and weight ($n = 256$), or with childhood medical conditions that might affect growth ($n = 95$ for diabetes, juvenile rheumatoid arthritis, inflammatory bowel disease, cerebral palsy, Down syndrome, acute lymphocytic leukaemia, other selected factitious, endocrine, metabolic, neurological, renal, respiratory (except asthma) and orthopaedic conditions, and congenital anomalies) In addition, we excluded offspring whose mothers had type 2 diabetes, cardiovascular diseases or cancer in 1989 ($n = 470$). The final population included 7946 female participants born to 7004 women, and 7063 male participants born to 6180 women.

Exposure

Maternal GDM status in the index pregnancy was self-reported in the GUTS mothers' supplementary questionnaire, the NHS II 1989 questionnaire and/or the NHS II 2009 lifetime pregnancy history questionnaire. In the GUTS supplementary questionnaire to mothers, women (i.e. participants in the NHSII) were asked if they had GDM for this index pregnancy. In the NHS II 2009 questionnaire, women were asked about all pregnancies and related complications. Based on the child's identification number and birth date and the woman's identification number, we linked information regarding the index pregnancy for each GUTS participant. For those who had GDM information missing on both the GUTS maternal supplementary and the NHS II 2009 questionnaires, we extracted information from the NHS II 1989 baseline questionnaire.[18] The concordance of three questionnaires was high (97%). Although information on GDM was self-reported, a previous validation study based on a randomly selected sample of women from the NHS II has shown good validity, with 94% of self-reported GDM cases being confirmed with medical records.[17]

Outcome

Offspring body mass index (BMI) was calculated based on height and weight self-reported annually between 1996 and 2001 and biennially between 2001 and 2010.[19–21] Overweight and obesity during childhood <18 years) were defined using age and sex-specific cutoffs based on the International Obesity Task Force criteria,[22] and during adulthood (≥ 18 years) using the World Health Organization cutoffs.[23] Previous studies had demonstrated that pre-adolescents,[24] adolescents and young adults can report their height and weight with good validity ($r \geq 0.87$ for weight and ≥ 0.82 for height).[25–27]

Covariates

From the GUTS study supplementary questionnaire, we obtained information on each child's birthweight, gestational age, medical conditions and duration of breastfeeding during infancy. In the 2009 NHS II questionnaire, women reported information on the year, gestational age at delivery, complications and outcomes of all previous pregnancies. To adjust for maternal adiposity, we extracted women's self-reported height and weight preceding the index pregnancy to calculate pre-pregnancy BMI.[28,29] Previous validation study had demonstrated high validity of self-reported height, weight and weight at age 18 years ($r = 0.94$ for height, $r = 0.97$ for weight and $r = 0.84$ for weight at age 18).[28,30]

Statistical analysis

An *a priori* sex-specific association between GDM and offspring adiposity status was examined. We used generalized linear model and generalized estimating equation for continuous (BMI) and binary (obesity status) outcomes, and specified correct variance-covariance structure to account for clustering within the same family. We *a priori* adjusted for maternal pre-pregnancy BMI, maternal age, geographical region and pre-pregnancy smoking status. We examined the association between GDM and offspring obesity across different age groups, from late childhood (age ≤ 12 years), adolescence ($12 < age < 18$ years), and through early adulthood (age ≥ 18 years). We generated an interaction term between GDM and offspring sex and tested for the significance of interaction using the Wald test.

To test the robustness of our findings, we conducted a series of sensitivity analyses. To minimize potential residual confounding from pre-pregnancy BMI, we further adjusted for it in more detailed categories (< 23, 23–25, 25–27, 27–30, 30–35, 35 + kg/m^2) and as a continuous variable, respectively. In addition, we estimated the joint

effect of GDM with pre-pregnancy BMI, a major risk factor for offspring obesity, by modelling combinations of GDM (yes, no) and BMI categories (BMI < 25, 25–29, or $30 + kg/m^2$). Moreover, we explored whether the observed association may potentially be mediated through birthweight.[31] To evaluate whether menarche status of female participants in the GUTS study modified the GDM-offspring obesity association, we performed stratified analysis by menarche status for female participants (pre-menarche and post-menarche). We also evaluated whether childhood factors (Tanner stage, total calories intakes, physical activity, alcohol consumption, smoking status, eating disorder, sugar-sweetened beverage consumption and TV watching) modified the association by stratified analyses. Finally, we additionally adjusted for other pregnancy complications (pre-eclampsia, gestational hypertension and caesarean section delivery), previous GDM history and paternal height to minimize the potential impact due to residual confounding by unmeasured variables. We further used bias formula method to evaluate whether the observed effects could be explained by unmeasured confounders.[32]

Results

Overall, among 7946 female offspring participants, 988 became obese during follow-up. Among 7063 male offspring, 1047 became obese. Offspring who were born to a GDM pregnancy were more likely to have high birthweight. Their mothers were more likely to be overweight or obese, and were more likely to have other pregnancy-related complications, such as hypertensive disorders during pregnancy (Table 1). Male participants who were born to a GDM pregnancy had higher BMI compared with males who were born to a non-GDM pregnancy, across all age groups; whereas BMI for female participants did not differ by maternal GDM status appreciably, across all age groups (Figure 1). The significant difference persisted even after adjustment for pre-pregnancy BMI and other covariates.

Similarly, intrauterine exposure to GDM was associated with a higher risk of obesity in the male but not the female offspring (P for interaction < 0.0001, Table 2). For male participants, GDM was associated with a 47% increase risk for offspring obesity after adjustment for pre-pregnancy BMI, maternal age, geographical region and pre-pregnancy smoking status (Table 2). Overall, pre-pregnancy BMI appeared to be the strongest confounder for the association between GDM and offspring obesity (Table 2). No significant association was observed for female participants. Results did not change considerably when pre-pregnancy BMI was modelled in six categories

(< 23, 23–25, 25–27, 27–30, 30–35, $35 + kg/m^2$) or as a continuous variable (data not shown).

We further examined the association of GDM with offspring risk of obesity at three critical developmental periods: late childhood, adolescence and early adulthood. For male participants, elevated risk of obesity was observed from late childhood through early adulthood: a 1.6-fold increased risk of obesity during late childhood, 1.5-fold during adolescence and 1.4-fold during early adulthood (Table 2). For female participants, no significant association was observed in any of the three developmental periods (Table 2). Moreover, the associations for female participants remained null regardless of menarche status (RR = 0.97; 95% CI: 0.71–1.34 for pre-menarche; RR = 1.02; 95% CI: 0.57–1.82 for post-menarche).

We observed significant interactions between GDM and pre-pregnancy BMI, in particular among male offspring (P for interaction = 0.0003 for male offspring, 0.6 for female offspring; Supplementary Figure 1, available as Supplementary data at *IJE* online). The highest risk group for male offspring was those born to GDM women who were obese before the index pregnancy; adjusted RR for them was 11.41 (95% CI: 4.92, 26.46) as compared with male offspring who were born to non-GDM women who were normal weight before pregnancy. Adjusted RR for female offspring was 3.8 (95% CI: 2.19, 6.65; Supplementary Figure 2, available as Supplementary data at *IJE* online).

In sensitivity analyses, the results on associations of GDM with offspring's risk of obesity were similar after additional adjustment for paternal height, previous GDM history, birthweight, pregnancy complications and offspring childhood characteristics. Notably, the mediating effect attributed to birthweight was not significant among either male or female offspring ($P = 0.91$ and 0.81, respectively; Supplementary Table 1, available as Supplementary data at *IJE* online). Sensitivity analyses also indicated that only under the condition of extreme unmeasured confounding could the observed elevated relative risk of 1.40 between GDM and offspring obesity among males be reduced to null. The unmeasured confounder would need to associated with both the risk of GDM and the risk of obesity by 2.1 fold each, above and beyond the measured confounders.

Discussion

In this prospective cohort study among 15 009 participants with 14 years of follow-up, we observed that maternal GDM was associated with a higher risk of obesity in late childhood, adolescence and early adulthood for male participants, but not for female participants. Furthermore, the

Table 1. Age-standardized baseline characteristics of offspring participants from the Growing Up Today Study (GUTS) and their mothers from the Nurses' Health Study II (NHSII)

	Female participants		Male participants	
	Born to GDM pregnancy	Born to non-GDM pregnancy	Born to GDM pregnancy	Born to non-GDM pregnancy
N	396	7550	360	6703
Maternal characteristics				
Age, years	29.6 (3.6)	29.4 (3.5)	29.5 (3.8)	29.4 (3.5)
Hypertensive disorder during pregnancy, %	9	3	7	3
Pre-eclampsia/toxaemia during pregnancy, %	7	4	8	4
Caesarean section, %	27	18	29	18
Pre-pregnancy body mass index (kg/m^2)	23.2 (4.4)	22.1 (3.3)	23.3 (4.2)	22.2 (3.5)
Body mass index at age 18 (kg/m^2)	21.1 (3.2)	20.9 (2.8)	21.3 (3.0)	21.0 (2.9)
Parity	1.7 (0.8)	1.8 (0.9)	1.7 (0.9)	1.7 (0.9)
Pre-pregnancy smoking, %				
Never smoker	69	70	70	70
Past smoker	9	9	7	8
Current smoker	22	21	23	22
Previous history of GDM, %	15	0	19	0
Breastfeeding duration				
Never breastfeeding, %	11	10	11	10
<1 month, %	7	5	5	5
1–9 months, %	50	47	47	45
>9 months, %	32	32	31	30
Offspring characteristics at birth				
Birthweight, %				
<5 pounds (2268 grams)	2	2	2	1
5–5.4 pounds (2449 grams)	1	2	1	1
5.5–6.9 pounds (3130 grams)	12	17	12	12
7–8.4 pounds (3810 grams)	60	61	49	58
8.5–9.9 pounds (4491 grams)	22	17	28	25
10+ pounds (4536 grams)	3	1	8	3
Birth order	1.6 (0.8)	1.7 (0.9)	1.8 (0.9)	1.7 (0.9)
Offspring characteristics at baseline (1996)				
Age	11.4 (1.5)	11.6 (1.6)	11.3 (1.6)	11.4 (1.6)
Current smoking, %	22	21	24	22
Race/ethnicity, White %	92	95	94	94
Body mass index (kg/m^2)	19.4 (3.6)	19.1 (3.5)	19.9 (4.1)	19.2 (3.5)
Body mass index change from 1996 to 2010 (kg/m^2)	4.5 (4.1)	4.3 (3.8)	4.6 (4.3)	4.6 (3.7)
Total caloric intake, kcal/day	2075 (711)	2044 (642)	2319 (767)	2287 (714)
Physical activity, MET h/week	15.4 (8.6)	16.1 (8.4)	15.8 (8.0)	16.5 (8.2)
Menstrual periods begun, %	34	34		
Alcohol intake, g/day	0.04 (0.3)	0.04 (0.4)	0.09 (0.9)	0.05 (0.4)

Values are means (SD) unless otherwise specified.

observed association among male offspring remained significant even after adjustment for pre-pregnancy BMI, a major risk factor not adequately adjusted for in a considerable number of previous studies.

The 'fetal programming theory' highlights the significance of investigating the long-term implication of suboptimal intrauterine exposure on offspring health.[33] Maternal hyperglycaemia can lead to fetal overnutrition, induce a pro-inflammatory state with increased oxidative stress,[34] modify methylation and expression of genes associated with appetite,[6,35,36] stimulate insulin secretion,[37] induce neurohormonal and epigenetic changes in the hypothalamus[37–39] and lead to high adiposity at birth,[3] which may subsequently set the offspring on a trajectory to obesity later in life.[2,33]

The association of GDM with offspring obesity risk has been investigated in a number of epidemiological studies.[7–9] Findings have been inconsistent, partly due to the different
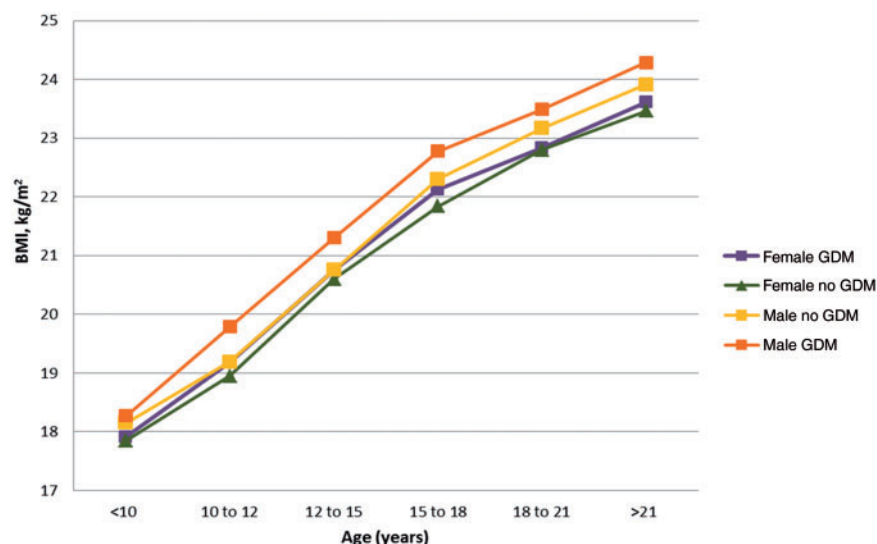
Figure 1. Body mass index of offspring born to a pregnancy with vs without gestational diabetes (GDM) by offspring sex.
Covariates in the multivariate model include age (continuous), maternal age (continuous), pre-pregnancy body mass index (BMI: < 24.99, 25–29, 30 + kg/m^2), geographical region (Northeast, Midwest, West, South) and pre-pregnancy smoking status (never, past, current).
Purple line indicates female offspring born from pregnancies complicated by GDM.
Green line indicates female offspring born from pregnancies uncomplicated by GDM.
Yellow line indicates male offspring born from pregnancies uncomplicated by GDM.
Orange line indicates male offspring born from pregnancies complicated by GDM.

Table 2. Multivariate adjusted relative risk (95% confidence interval)[a] for the association between maternal gestational diabetes and sex-specific offspring risk of obesity

		All	Female participants	Male participants
All[a,*]	Obesity cases (N)	2035	988	1047
	Age-adjusted model[b]	1.45 (1.16–1.80)	1.19 (0.88–1.63)	1.69 (1.26–2.26)
	Multivariate model[c]	1.28 (1.04–1.58)	0.94 (0.69–1.27)	1.61 (1.23–2.10)
	Multivariate model[d]	1.23 (0.99–1.52)	0.97 (0.71–1.33)	1.47 (1.11–1.95)
Age < 12 years	Obesity cases (N)	590	264	326
	Multivariate model[d]	1.29 (0.92–1.81)	0.95 (0.53–1.71)	1.59 (1.05–2.41)
12 ≤ age < 18 years	Obesity cases (N)	1181	509	672
	Multivariate model[d]	1.19 (0.91–1.56)	0.87 (0.57–1.32)	1.48 (1.06–2.06)
Age ≥ 18 years	Obesity cases (N)	1541	785	756
	Multivariate model[d]	1.22 (0.96–1.54)	1.06 (0.77–1.46)	1.39 (1.00–1.94)

[a]Relative risk using offspring born to non-GDM women as the reference group.

[b]Age-adjusted model: age (continuous).

[c]Multivariate model: age (continuous), pre-pregnancy body mass index <24.99, 25–29, 30 + kg/m^2).

[d]Multivariate model: age (continuous), pre-pregnancy body mass index (<24.99, 25–29, 30 + kg/m^2), maternal age (continuous), geographical region (Northeast, Midwest, West, South) and pre-pregnancy smoking status (never, past, current).

*P for interaction by offspring sex < 0.0001.

age groups examined and confounding factors adjusted for. Moreover, pre-pregnancy BMI, an important confounder for this association, was appropriately accounted for in few studies.[7–9] Furthermore, the majority of the literature focused on early childhood; studies with long-term follow-up of the offspring through adolescence and adulthood are extremely sparse.[40, 41] The elevated risk of obesity among male participants in our study was consistent with a large sibling study among Swedish men at age 18.[42] However, the Swedish study only included male participants. Further, findings from sensitivity analysis suggested that birthweight only accounted for a minimal proportion of the association between GDM and offspring obesity. This observation is consistent with previous data reporting that birthweight did not markedly attenuate the association of interest.[14,19,43,44] Taken together, these data suggest that GDM may predispose offspring to increased risk of obesity in later life via mechanisms beyond excessive fetal growth, as indicated by birthweight.

Our findings of a sex-specific association of maternal GDM with increased risk of obesity among male offspring are in line with emerging evidence supporting the sex-specific effect of maternal glycaemia on offspring cardio-metabolic phenotype. It was observed that glycaemic level strongly predicted adiposity for male infants but not for female infants.[45] Male participants of GDM mothers had higher adiposity at age 8 years, but not their female counterparts.[14] Similarly among a Spanish population, GDM was associated with macrosomia only among male newborns but not among females.[13] Moreover, some biological evidence suggested that placentas of male fetuses are more efficient and have less reserve capacity than placentas of female fetuses.[11] In the womb, male fetuses grow faster and are more sensitive to stressful events and maternal pregnancy diet compared with female fetuses.[3,46,47] Some additional evidence suggests sex differences in metabolic function, epigenetics and paediatric obesity risk.[48–53] Despite these findings, long-term sex-specific effects of GDM on offspring obesity, particularly beyond early childhood, among humans is largely unknown. The existing studies were of short duration of follow-up (mean age of the offspring was less than 8 years) and small sample size. Data from the present study provided the evidence that long-term impacts of GDM on offspring obesity risk may differ by sex, with an elevated risk being evident only among male participants from late childhood through early adulthood, which may be used to inform obesity intervention strategies among high-risk children born to women with GDM. Specifically, sex-specific interventions may be warranted, particularly targeting boys as early as childhood. Moreover, despite the overall null association among girls, the positive although non-significant association between intrauterine exposure to GDM and risk of obesity at 18 years and above might suggest a delayed onset of increased obesity risk. Longitudinal data with longer follow-up beyond early adulthood are warranted.

Strengths of our study include large sample size, long-term follow up and repeated measurement of weight and lifestyle information prospectively collected for both mothers and offspring. Moreover, we have been able to follow offspring up until early adulthood and were able to examine the long-term influences of GDM on offspring obesity. Moreover, detailed information was collected on pre-pregnancy BMI, which was not adequately adjusted for in many previous studies.[12,13] Further, we have extensive information on pregnancy complications, detailed information on lifetime pregnancy history and were able to identify GDM status for the index pregnancy. For our analytical approach, we accounted for clustering within the family and were able to examine the association in late childhood, adolescence and early adulthood, respectively.

Several potential limitations merit discussion. GDM was a self-reported physician diagnosis. However, a previous validation study demonstrated that self-reported GDM status by nurses has good validity and accuracy.[28] Our study participants were all offspring of nurses from the NHS II which, by design, reduces confounding by socioeconomic factors. The majority of our study participants were mostly non-Hispanic White with relatively high or average socioeconomic status. Future studies among other race/ethnicities and low socioeconomic groups are warranted. Height and weight were self-reported by the study participants and measurement errors are inevitable. However, previous studies have shown reasonable validity for self-reported height and weight among adolescents.[34,35]

In this large long-term prospective cohort of US women and their offspring, exposure to GDM *in utero* was associated with increased risk of obesity for male participants only. The elevated risk persisted across late childhood, adolescence and early adulthood. Further studies are warranted to confirm these findings in other populations, in particular of other race/ethnicities, and to elucidate the underlying biological mechanisms.

Supplementary Data

Supplementary data are available at *IJE* online.

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