

Original Article

Maternal obesity, gestational weight gain, and offspring asthma and atopy



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ABSTRACT

Background: Maternal obesity may affect offspring asthma and atopic disease risk by altering fetal immune system development. However, few studies evaluate gestational weight gain (GWG).

Objective: To evaluate relationships between maternal body mass index (BMI), GWG, and persistent wheeze, eczema, allergy, and asthma risk in offspring through middle childhood.

Methods: A total of 5939 children from Upstate KIDS, a population-based longitudinal cohort of children born in upstate New York (2008–2019) were included in the analysis. Persistent wheeze or asthma, eczema, and allergy were maternally reported at multiple study time points throughout early and middle childhood. Poisson regression models with robust SEs were used to estimate adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) for offspring atopic outcomes by maternal prepregnancy BMI and GWG.

Results: Prepregnancy BMI was associated with increased risk of persistent wheeze by 3 years of age even after adjustments for maternal atopy (class I obesity: aRR, 1.58; 95% CI, 1.13–2.20; class II or III obesity: aRR, 1.69; 95% CI, 1.22–2.35). Associations with reported asthma in middle childhood did not reach statistical significance. Furthermore, no associations were found between prepregnancy BMI and atopic outcomes in either early or middle childhood. GWG was not associated with higher risk of early childhood persistent wheeze or middle childhood asthma.

Conclusion: Maternal prepregnancy BMI was associated with increased risk of offspring wheeze, whereas excessive GWG was generally not associated with childhood asthma or atopy.

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Introduction

Prevalence of maternal obesity, high gestational weight gain (GWG), and atopic disease has increased in the past several

decades.^{1–3} Approximately 30% of women of reproductive age in the United States are obese, and a growing body of research has documented numerous adverse health outcomes in the offspring of women with obesity.¹ Similarly, 47.2% and 20.9% of women had excessive or inadequate GWG, respectively, based on the guidelines of the Institute of Medicine (IoM, recently renamed the National Academies of Medicine).^{4,5} Obesity is widely considered a state of low-grade chronic inflammation, marked by higher levels of cytokines and C-reactive protein. In line with the developmental origins of health and disease hypothesis, prenatal exposures to maternal obesity may have implications for development of the immune system of the offspring in utero.⁶

Concurrently, there is concerning evidence of increasing global prevalence of atopic diseases that may be related to socioeconomic determinants of health, such as obesity.^{2,7,8} Atopic diseases are

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immunoglobulin (Ig)E-mediated conditions, such as atopic dermatitis or eczema, food allergy, and allergic asthma. Prevalence of food allergy has increased up to 10% in recent years, and the estimated prevalence of atopic dermatitis among US children is 13%.^{9,10} In addition, asthma is one of the most common chronic conditions among children, and though asthma consisted of multiple clinical phenotypes, childhood-onset asthma typically fits in to the allergic phenotype.¹¹ Such allergic diseases are rarely fatal, but they can have substantial impact on quality of life and may increase incidence of more serious conditions in adulthood.^{6,12} Although atopic diseases may manifest symptoms as a result of sensitization to environmental risk factors, research has revealed that perinatal exposures may increase susceptibility to sensitization and progression of the “atopic march.”^{7,13}

Meta-analyses have reported fairly consistent evidence for increased risks of childhood asthma or wheeze associated with pre-pregnancy obesity.^{14–16} Though fewer studies have evaluated the effects of GWG on other non-asthma outcomes. For instance, a recent meta-analysis explored associations of body mass index (BMI) and GWG with atopic dermatitis outcomes in offspring, in which high or excessive GWG was associated with an increased risk.¹⁷ However, this finding was based on only 2 studies evaluating GWG exposure in that meta-analysis and more recent findings found no associations between GWG and atopic dermatitis.^{18,19} If GWG places offspring at increased risk of atopic disease, modifying weight gain has the potential to decrease morbidity and GWG can be used to identify and monitor offspring at high risk. Therefore, we evaluated the associations of prepregnancy BMI and GWG on both asthma and other atopic outcomes, including eczema or atopic dermatitis, through middle childhood in a prospective cohort study.

Methods

Study Population

Our study used data on maternal weight, lifestyle factors, and allergic disease in offspring collected in the Upstate KIDS Study, a large, population-based longitudinal cohort study of 5034 pregnancies and 6171 offspring born in New York State (excluding New York City). Details of the sampling framework and recruitment procedures can be found elsewhere.²⁰ Briefly, participants were recruited using the New York State livebirth registry to identify eligible children born between 2008 and 2010. All children conceived using fertility treatments as recorded on birth certificates were invited to participate in the study, as were all children of multiple births regardless of conception method. Children not conceived using fertility treatments were frequency matched to area of residence of those who were conceived using treatments at a 3:1 ratio. Follow-up of this cohort continued until 2019. The New York State Department of Health and the University at Albany Institutional Review Boards approved the study, serving as the institutional review board designated by the National Institutes of Health under a reliance agreement. Parents provided written informed consent.

Measurements

Maternal Obesity and Gestational Weight Gain

Maternal prepregnancy BMI was calculated using prepregnancy weight and height as provided in the birth certificate. If data were missing, maternal questionnaire data from 4 months postpartum were used. We evaluated BMI categorically as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese class I (30–34.9 kg/m²), or obese class II or III (≥35 kg/m²). The GWG was self-reported on maternal questionnaires. Categories of GWG were defined using the 2009 IoM guidelines.⁵ Adequate weight gain for singleton pregnancies was defined as 28 to 40, 25 to

35, 15 to 25, and 11 to 20 pounds total GWG for underweight, normal weight, overweight, or obese women, respectively. The GWG guidelines of adequate weight gain for women with twin gestations were defined as 37 to 54, 31 to 50, and 25 to 42 pounds for women of normal weight, overweight, or obesity, respectively. The GWG above or below these guidelines was categorized as excessive or inadequate.

Atopy

Data on infant wheeze, eczema or atopic dermatitis, and allergies were captured through maternal report on study questionnaires completed in early childhood. Persistent wheeze was defined as any 2 reports of wheeze at 4, 8, 12, 18, 24, 30, or 36 months of age. Eczema or atopic dermatitis was defined as any maternal report of physician-diagnosed eczema or atopic dermatitis at 8, 12, 18, 24, 30, or 36 months of age. Mothers were also asked to report if their toddler had a physician-diagnosed allergy to food, medicine, dust, animals, pollen, or ragweed at 8, 12, 18, 24, 30, or 36 months of age. For analysis of early childhood outcomes, we evaluated any atopy, as defined by any reported allergy, eczema or atopic dermatitis, or food allergy by 36 months of age.

Middle childhood outcomes of asthma, eczema or atopic dermatitis, and allergies were evaluated at approximately 7, 8, or 9 years of age when mothers completed questionnaires annually between 2016 and 2019. In middle childhood, asthma was defined as any maternal report of current physician-diagnosed asthma or prescription of asthma medication or inhaler in the past year. Eczema was defined as any report of physician-diagnosed eczema. Last, allergies were defined as any report of seeing a physician for allergy or use of allergy medication in the past year.

Covariates

Maternal age at delivery, race and ethnicity, educational level, health insurance status data, and offspring birthweight and gestational age were collected from the birth certificate. Maternal atopy (defined by history of asthma, eczema, or allergy to food or pollen), marital status, and maternal smoking habits were reported by mothers at 4 months postpartum. Gestational diabetes was based on indication in vital statistics records, discharge diagnoses derived from the Statewide Planning and Research Cooperative System (SPARCS), or maternal self-report at 4 months postpartum.

Statistical Analyses

We calculated descriptive statistics to evaluate distributions of the demographic and biological characteristics of participants by prepregnancy BMI categories and GWG categories. These comparisons were made at the family level ($n = 4912$) to avoid double counting information from families with twins. We used Poisson regression models with robust SEs to estimate the relative risks (RRs) and 95% confidence intervals (CIs) for the association between prepregnancy BMI, GWG, and atopic outcomes in unadjusted and multivariable adjusted models. Models included a random effect to account for the dependence between twins of the same family and were adjusted for maternal age, race and ethnicity, education, marital status, smoking during pregnancy, private health insurance, maternal history of atopy, and plurality based on a priori mapping of causal relationships between exposures and outcomes using a directed acyclic graph. Models evaluating GWG as an exposure were also adjusted for maternal prepregnancy BMI and gestational age.

Because infants conceived by fertility treatment and twins were oversampled in this study, we used sampling weights in each model to account for this study design feature.²⁰ To account for missing outcome data, we used inverse probability weighting. Sampling and

inverse probability treatment weights were multiplied and then trimmed at the 95th percentile for analyses. To account for missing covariate data, 50 data sets were created using multiple imputation by chained equations.

Sensitivity analyses were performed. First, we used International Classification of Diseases, Ninth Revision (ICD-9), codes to identify early childhood asthma and allergy-related conditions as registered in the SPARCS. SPARCS is a longitudinal inpatient and outpatient hospital discharge data system from the state of New York and would likely reflect the more severe cases of asthma or allergy. The ICD-9 codes for asthma and allergy-related conditions are provided in eTable 1. We conducted a survival analysis to assess if the time to asthma or allergy based on the first reported ICD-9 code differs by categories of maternal prepregnancy BMI and GWG. The time scale was the child's age in months as reported in SPARCS, and participants were right censored at the end of the SPARCS linkage (age 40 months). We obtained Kaplan-Meier curves and log-rank *P* values. Second, we evaluated associations of GWG with early and middle childhood atopic outcomes stratified by plurality status as previous literature suggests that twins may be at an increased risk of early life wheeze or asthma.

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Prepregnancy BMI and GWG differed by maternal age, education, marital status, smoking during pregnancy, insurance status, and gestational diabetes (Table 1). Prepregnancy BMI was also associated with maternal atopy, and GWG was further associated with plurality and gestational age. By age 3 years, 10.8% of toddlers were reported

to have persistent wheeze, 39.2% any atopy, 28.2% eczema or atopic dermatitis, and 10.2% any food allergy. Most infants with persistent wheeze had 1 to 2 reported wheeze attacks at each assessment. In SPARCS, 145 (3.8%) had at least 1 ICD-9 code consistent with an asthma-related condition and 34 (0.9%) had at least 1 ICD-9 code consistent with any allergy-related condition through 40 months of follow-up. By middle childhood, 16.5% of children had current asthma (physician diagnosis or medication in past year), 10.4% eczema, 16.7% with physician-diagnosed allergies in past year, and 14.2% allergy medication prescribed in past year.

Table 2 presents the associations of prepregnancy BMI categories and atopy outcomes in early and middle childhood. We observed an increased risk of persistent wheeze among offspring of mothers with class I obesity (adjusted risk ratio [aRR], 1.45; 95% CI, 1.03–2.03) and class II or III obesity (aRR, 1.51; 95% CI, 1.08–2.11) as compared with normal weight before pregnancy. A borderline association for maternal class II or III obesity (aRR, 0.81; 95% CI, 0.66–1.00) but not class I obesity (aRR, 1.03; 95% CI, 0.87–1.22) was associated with decreased risk of eczema or atopic dermatitis in early childhood. No statistically significant effects were observed with food allergy or atopy overall in early childhood. By middle childhood, we found no significant associations with asthma or eczema in the adjusted models. Prepregnancy BMI was positively associated with reported allergy at 7 to 9 years, but not use of allergy medication use. Children of women with overweight prepregnancy BMI were more likely to have reported allergy than children of women with normal prepregnancy BMI (aRR, 1.72; 95% CI, 1.18–2.51). A similar trend was observed among children of women with class I or class II or III obesity though these associations did not reach statistical significance.

Table 3 presents the associations of GWG based on IoM guidelines and atopy outcomes in early and middle childhood, in which, we found no associations with persistent wheeze, asthma, or eczema. In

Table 1
Baseline Characteristics (n [%] or mean $\pm$ SD) by Maternal Prepregnancy BMI or Gestational Weight Gain

Characteristic	Maternal prepregnancy BMI					Gestational weight gain		
	<18.5	18.5–24.9	25–29.9	30–34.9	≥ 35	Inadequate	Adequate	Excessive
N (%)	125 (2.6)	2225 (45.4)	1254 (25.6)	650 (13.3)	648 (13.2)	1691 (34.6)	1055 (21.6)	2141 (43.8)
Maternal age (y) ^{a,b}	28.4 $\pm$ 7.0	30.5 $\pm$ 6.0	30.9 $\pm$ 6.2	30.2 $\pm$ 5.9	30.0 $\pm$ 5.7	31 $\pm$ 6.0	30.8 $\pm$ 6.1	29.9 $\pm$ 6.0
Maternal prepregnancy BMI (kg/m ²) ^b	—	—	—	—	—	25.7 $\pm$ 6.2	28 $\pm$ 8.4	27.7 $\pm$ 6.3
Race and ethnicity								
White	98 (78.4)	1803 (81.0)	997 (79.5)	531 (81.7)	514 (79.3)	1362 (80.5)	823 (78.0)	1748 (81.6)
Other ^c	27 (21.6)	422 (19.0)	257 (20.5)	119 (18.3)	134 (20.7)	329 (19.5)	232 (22.0)	393 (18.4)
Education ^{a,b}								
Less than college	63 (50.4)	926 (41.6)	606 (48.3)	380 (58.5)	445 (68.7)	749 (44.3)	558 (52.9)	1102 (51.5)
College	62 (49.6)	1299 (58.4)	648 (51.7)	270 (41.5)	203 (31.3)	942 (55.7)	497 (47.1)	1039 (48.5)
Marital status ^{a,b}								
Not married	19 (15.7)	208 (9.8)	142 (11.8)	76 (12.2)	103 (16.4)	147 (9.1)	131 (12.8)	268 (13.0)
Married	102 (84.3)	1923 (90.2)	1062 (88.2)	546 (87.8)	526 (83.6)	1466 (90.9)	889 (87.2)	1793 (87.0)
Smoking during pregnancy ^{a,b}								
No	93 (74.4)	1958 (88.0)	1085 (86.5)	554 (85.4)	520 (80.2)	1509 (89.2)	885 (83.9)	1804 (84.3)
Yes	32 (25.6)	267 (12.0)	169 (13.5)	95 (14.6)	128 (19.8)	182 (10.8)	170 (16.1)	336 (15.7)
Private insurance ^{a,b}								
No	46 (36.8)	499 (22.4)	296 (23.6)	178 (27.4)	206 (31.8)	368 (21.8)	267 (25.3)	582 (27.2)
Yes	79 (63.2)	1724 (77.6)	957 (76.4)	471 (72.6)	442 (68.2)	1322 (78.2)	787 (74.7)	1557 (72.8)
Gestational diabetes mellitus ^{a,b}								
No	121 (96.8)	2094 (94.1)	1130 (90.1)	565 (86.9)	521 (80.4)	1541 (91.1)	926 (87.8)	1950 (91.1)
Yes	4 (3.2)	131 (5.9)	124 (9.9)	85 (13.1)	127 (19.6)	150 (8.9)	129 (12.2)	191 (8.9)
Maternal atopy ^a								
No	92 (75.4)	1510 (69.7)	831 (68.1)	369 (58.5)	347 (54.4)	1116 (68.0)	674 (65.2)	1348 (64.5)
Yes	30 (24.6)	657 (30.3)	389 (31.9)	262 (41.5)	291 (45.6)	524 (32.0)	359 (34.8)	743 (35.5)
Plurality ^b								
Singletons	104 (83.2)	1752 (78.7)	973 (77.6)	506 (77.8)	492 (75.9)	1218 (72.0)	661 (62.7)	1934 (90.3)
Twins	21 (16.8)	473 (21.3)	281 (22.4)	144 (22.2)	156 (24.1)	473 (28.0)	394 (37.3)	207 (9.7)
Gestational age (wk) ^b	37.9 $\pm$ 2.8	38.1 $\pm$ 2.4	38.1 $\pm$ 2.4	38.1 $\pm$ 2.4	37.9 $\pm$ 2.6	37.9 $\pm$ 2.4	37 $\pm$ 3.2	38.7 $\pm$ 1.8

Abbreviation: BMI, body mass index.

^a*P* value < .05 in comparison among maternal prepregnancy BMI.

^b*P* value < .05 in comparison among gestational weight gain.

^cOther race/ethnicity: non-Hispanic Black (4.9%); non-Hispanic Asian (2.7%); Hispanic (5.9%); multiracial/other race (6.2%).

Table 2
Associations of Maternal Prepregnancy BMI Categories and Asthma and Other Atopic Outcomes

Outcome	Maternal prepregnancy BMI				
	<18.5	18.5–24.9	25–29.9	30–34.9	≥35
Early childhood (4–36 mo)					
Persistent wheeze, N (%)	14 (11.20)	210 (9.03)	135 (10.59)	84 (13.46)	99 (15.16)
Unadjusted	0.89 (0.40, 1.96)	REF	1.27 (0.95, 1.70)	1.58 (1.13, 2.20)	1.69 (1.22, 2.35)
Adjusted	0.93 (0.42, 2.09)	REF	1.24 (0.93, 1.65)	1.45 (1.03, 2.03)	1.51 (1.08, 2.11)
Any atopy, N (%)	57 (39.04)	1119 (41.86)	578 (38.00)	288 (36.55)	281 (35.17)
Unadjusted	0.96 (0.73, 1.26)	REF	0.99 (0.89, 1.11)	0.97 (0.84, 1.11)	0.83 (0.71, 0.97)
Adjusted	1.04 (0.79, 1.37)	REF	1.01 (0.91, 1.13)	1.00 (0.87, 1.15)	0.89 (0.76, 1.04)
Eczema or atopic dermatitis, N (%)	39 (26.71)	820 (30.68)	411 (27.02)	213 (27.03)	191 (23.90)
Unadjusted	0.84 (0.57, 1.23)	REF	0.97 (0.85, 1.12)	1.00 (0.84, 1.19)	0.76 (0.62, 0.93)
Adjusted	0.95 (0.65, 1.38)	REF	0.99 (0.86, 1.14)	1.03 (0.87, 1.22)	0.81 (0.66, 1.00)
Food allergies, N (%)	14 (11.11)	250 (10.56)	126 (9.66)	67 (10.45)	67 (9.99)
Unadjusted	1.22 (0.65, 2.31)	REF	0.97 (0.73, 1.28)	0.88 (0.60, 1.27)	0.90 (0.62, 1.31)
Adjusted	1.32 (0.70, 2.50)	REF	0.97 (0.73, 1.28)	0.84 (0.57, 1.23)	0.89 (0.61, 1.31)
Middle childhood (7–9 y)					
Any asthma, N (%)	13 (23.64)	137 (13.88)	86 (17.41)	42 (17.00)	60 (22.22)
Unadjusted	1.79 (0.93, 3.43)	REF	1.40 (0.99, 1.97)	1.23 (0.78, 1.94)	1.53 (1.02, 2.32)
Adjusted	1.62 (0.85, 3.06)	REF	1.28 (0.92, 1.78)	1.05 (0.67, 1.64)	1.12 (0.74, 1.70)
Current eczema, N (%)	5 (9.09)	110 (11.20)	50 (10.16)	19 (7.72)	29 (10.78)
Unadjusted	0.87 (0.30, 2.50)	REF	0.99 (0.61, 1.59)	0.69 (0.33, 1.42)	1.15 (0.63, 2.09)
Adjusted	0.84 (0.28, 2.46)	REF	0.92 (0.57, 1.48)	0.59 (0.28, 1.25)	0.93 (0.49, 1.74)
Current allergy (report), N (%)	7 (15.56)	109 (13.31)	84 (21.00)	33 (17.10)	43 (21.61)
Unadjusted	1.49 (0.61, 3.61)	REF	1.70 (1.16, 2.49)	1.44 (0.85, 2.46)	1.48 (0.87, 2.52)
Adjusted	1.49 (0.63, 3.51)	REF	1.72 (1.18, 2.51)	1.52 (0.89, 2.61)	1.52 (0.89, 2.59)
Current allergy (prescription), N (%)	9 (16.36)	124 (12.63)	73 (14.84)	37 (15.10)	47 (17.60)
Unadjusted	1.12 (0.49, 2.56)	REF	1.32 (0.90, 1.92)	1.17 (0.72, 1.92)	1.40 (0.88, 2.21)
Adjusted	0.93 (0.39, 2.20)	REF	1.17 (0.81, 1.69)	1.01 (0.62, 1.65)	1.01 (0.63, 1.63)

Abbreviations: BMI, body mass index; CI, confidence interval; REF, reference; RR, relative risk.

NOTE. Unadjusted and adjusted RRs and 95% CIs reported.

Adjusted model covariates: maternal age, race/ethnicity, education, marital status, smoking, private insurance, plurality, and maternal atopy.

Bold values indicate statistical significance.

Table 3
Associations of Maternal Gestational Weight Gain and Asthma and Other Atopic Outcomes

Outcome	Gestational Weight Gain		
	Inadequate	Adequate	Excessive
Early childhood (4–36 mo)			
Persistent wheeze, N (%)	151 (12.67)	178 (9.85)	212 (10.66)
Unadjusted	1.11 (0.81, 1.53)	REF	0.98 (0.76, 1.27)
Adjusted	1.00 (0.72, 1.38)	REF	0.93 (0.71, 1.21)
Any atopy, N (%)	549 (38.28)	818 (38.22)	953 (40.78)
Unadjusted	0.92 (0.81, 1.06)	REF	1.03 (0.93, 1.14)
Adjusted	0.98 (0.86, 1.12)	REF	1.08 (0.98, 1.20)
Eczema or atopic dermatitis, N (%)	380 (26.50)	630 (29.44)	662 (28.33)
Unadjusted	0.80 (0.68, 0.95)	REF	0.91 (0.80, 1.03)
Adjusted	0.86 (0.73, 1.02)	REF	0.96 (0.84, 1.09)
Food allergies, N (%)	109 (8.90)	188 (10.18)	226 (11.16)
Unadjusted	0.63 (0.43, 0.91)	REF	1.02 (0.80, 1.31)
Adjusted	0.64 (0.44, 0.94)	REF	1.05 (0.82, 1.36)
Middle childhood (7–9 y)			
Any asthma, N (%)	92 (19.74)	108 (14.04)	138 (16.93)
Unadjusted	1.39 (0.93, 2.07)	REF	1.14 (0.82, 1.58)
Adjusted	1.26 (0.84, 1.91)	REF	1.00 (0.72, 1.39)
Current eczema, N (%)	46 (9.91)	84 (10.99)	83 (10.21)
Unadjusted	0.80 (0.45, 1.39)	REF	0.90 (0.58, 1.38)
Adjusted	0.79 (0.43, 1.44)	REF	0.84 (0.54, 1.33)
Current allergy (report), N (%)	61 (15.76)	92 (14.81)	123 (19.04)
Unadjusted	1.35 (0.82, 2.24)	REF	1.52 (1.03, 2.25)
Adjusted	1.28 (0.77, 2.12)	REF	1.40 (0.93, 2.11)
Current allergy (prescription), N (%)	63 (13.55)	105 (13.80)	122 (15.02)
Unadjusted	1.05 (0.65, 1.69)	REF	1.14 (0.80, 1.61)
Adjusted	0.94 (0.59, 1.49)	REF	1.01 (0.70, 1.46)

Abbreviations: BMI, body mass index; CI, confidence interval; REF, reference; RR, relative risk.

NOTE. RRs and 95% CIs are reported.

Adjusted model covariates: maternal age, race/ethnicity, education, marital status, smoking, private insurance, plurality, maternal atopy, prepregnancy BMI, and gestational age.

Bold values indicate statistical significance.

analyses evaluating early childhood allergies to foods only, offspring of women with GWG below IoM guidelines had a decreased risk of developing food allergies by 36 months compared with offspring of women with GWG within the guidelines (aRR, 0.64; 95% CI, 0.44–0.94). Notably, after a Bonferroni *P* value adjustment for multiple comparisons, this association did not reach statistical significance. In the sensitivity analysis, in which we stratified by plurality status, we found that this association held in singletons (RR, 0.63; 95% CI, 0.42–0.95) but was limited in precision in the twins (RR, 0.76; 95% CI, 0.49–1.19). No other statistically significant differences in outcomes by GWG or prepregnancy BMI were found when repeating our analysis in singletons (eTable 2) and twins (eTable 3) separately.

Last, in our sensitivity analysis reflecting the more severe cases of early childhood asthma or allergy in our cohort, we did not find statistically significant associations with prepregnancy BMI and any severe allergy requiring in or out-patient hospital care (log-rank *P* value = .38) (eFig 1) or with asthma requiring in or out-patient care (log-rank *P* value = .70) (eFig 2). Nor did we find associations with GWG and severe allergy episode (log-rank *P* value = .14) (eFig 3) or asthma-related ICD-9 codes (log-rank *P* value = .53) (eFig 4).

Discussion

In our population-based, longitudinal cohort, we found evidence that prepregnancy obesity was associated with increased risks of persistent wheeze by 3 years of age but not asthma in middle childhood nor hospital visits due to asthma. Prepregnancy overweight may have a positive but lesser effect on persistent wheeze. A higher prepregnancy BMI was also consistent with elevated maternal report of offspring allergy in middle childhood but was not associated with early childhood allergy. GWG was generally not associated with offspring persistent wheeze or asthma. We did observe that children born to mothers with inadequate GWG had a modest decreased risk of food-related allergies in early childhood, but this finding did not withstand adjustment for multiple testing by Bonferroni correction (*P* < .01) and should be interpreted cautiously. Neither inadequate nor excessive weight gain was associated with middle childhood atopy outcomes.

Our findings regarding a modest elevated risk of persistent wheeze among children of women with higher prepregnancy BMI, particularly BMI of 30 or more, is consistent with previous studies, including a recent meta-analysis of 22 studies by Liu et al that evaluated wheeze and asthma outcomes,^{16,18,21–33} though our findings by middle childhood suggest no positive associations between prepregnancy BMI and asthma after adjustment for potential confounders. Fewer studies have evaluated GWG and offspring wheeze or asthma and Liu et al¹⁶ identified differences in findings based on how GWG was defined. High or low GWG categories (not based on IoM recommendations) were positively associated with childhood asthma or wheeze. However, when GWG was assessed according to IoM recommendations (like our study), Liu et al found a nonsignificant statistical inverse association between excessive GWG and asthma or wheeze based on 3 studies (average ages were 1, 4, and 6).^{16,29,32,34} Furthermore, 2 recent analyses by Srugo et al¹⁸ and Wei et al¹⁹ also reported no associations between GWG according to IoM guidelines and asthma or wheeze outcomes. These findings are consistent with our findings of GWG and persistent wheeze or asthma in early and middle childhood.

Studies evaluating the associations of atopic diseases, such as eczema or food allergy, with prepregnancy BMI or GWG have had mixed results.^{17–19,24,28,33} A meta-analysis by Chen et al,¹⁷ reported prepregnancy overweight and obesity were protective in the development of atopic dermatitis based on 6 to 7 studies (effect sizes ranging from 0.80 to 1.09 for children 3–17 years). In addition, Goudarzi et al²⁸ observed a protective effect of maternal BMI on eczema at age

7 years within a Japanese birth cohort. We similarly noted eczema effect sizes of 0.81 and 0.93 in the class II or III obesity adjusted models for early and middle childhood, respectively. In this same meta-analysis, Chen et al^{17,33} revealed that high or excessive GWG was associated with an increased risk of atopic dermatitis, whereas, low or inadequate GWG was associated with a decreased risk based only on 2 to 3 studies.^{23,35} Two more recent studies reported no associations between GWG and atopic dermatitis outcomes, similar to our findings in early and middle childhood.^{18,19} Few studies have evaluated food allergy outcomes. Similar to Kumar et al,²⁴ we found no association of food allergy with prepregnancy BMI. Yet, in a recent cross-sectional study of more than 8000 children, prepregnancy overweight or obesity was associated with an increased likelihood of food allergy in offspring aged 3 to 14 years.³³ That same study also found that children born to mothers with inadequate GWG based on IoM guidelines were less likely to have food allergy, which is consistent with the direction of our results. Though after stratifying for BMI, the association did not remain.³³

Several biological pathways explaining the relationship between maternal weight and offspring atopy have been hypothesized.^{36,37} One pathway may involve the downstream impact of prepregnancy obesity on exposure to inflammation, which in turn may have implications for the offspring microbiome.^{6,38–41} Nutrients are transported to the fetus through the placenta, which may play an important role in immune system development. Increased levels of lipids in the placentas of women with obesity may cause increases in macrophages and inflammatory factors.⁶ Studies of infants born to women with obesity have also observed elevated levels of numerous inflammatory cytokines, such as leptin and TNF- α in their cord blood, which is also associated with wheeze in children.³⁰ In Upstate KIDS, we reported no associations between maternal obesity or GWG with IgE concentrations—through which atopic reactions can be mediated—in newborn dried blood spots, but levels of inflammatory markers were associated with having BMI of 35 or more.⁴² During the birth process, newborn immunoglobulins and inflammatory markers can have high variability in response to birth stress, potentially making associations with prepregnancy BMI or GWG difficult to detect.⁴³ Evidence from other studies of maternal obesity and allergic sensitization is mixed, with a report of maternal obesity not associated with allergic sensitization in offspring, whereas another study reports an association between maternal obesity and decreased cord blood IgE.^{22,24} Maternal obesity can also increase the offspring's own risk of obesity, which is in turn a risk factor for wheezing and asthma.³⁰ Furthermore, research into the microbiomes of obese mothers and their offspring suggests that changes in the gut microbiome may play a role in infant immune development and risk of allergy and atopic disease.^{30,44} Taken together, these findings suggest that prepregnancy weight and GWG may be related to allergic disease through complex, multifactorial pathways. Better characterization of this relationship will also provide more complete scientific evidence for future GWG guideline development.

The strengths of this study include the longitudinal design and follow-up through middle childhood. Our study has several limitations. First, the study was not designed with the intent to clinically validate diagnoses of atopic disease. Outcome data were based on maternal self-report of physician's diagnoses which may be inaccurate. Misclassification of this type would likely add non-differential measurement error in the outcome, which might limit our ability to detect an association. Second, GWG is only measured across the entirety of the pregnancy, with no trimester-specific measurements available, though gestational age was accounted for in the models. Third, as this was an observational study, residual confounding cannot be ruled out; however, we were able to measure and adjust for numerous lifestyle and demographic characteristics measured in the baseline questionnaire (before reports of atopy) that were confirmed in subsequent follow-up questionnaires. Finally, the associations

presented do not imply causality and more studies are needed to help establish a causal relationship between prepregnancy BMI, GWG, and risk of atopy in the offspring.

Conclusion

Reports of prepregnancy obesity, high GWG, and allergic disease have increased in the past 20 years. In our population-based, longitudinal birth cohort study, we found that children of mothers with higher BMIs had higher risk of persistent wheeze in early childhood. The role of gestational weight gain remains unclear and requires potentially more information on timing of weight gain. Future studies should explore these relationships in different settings with physician-validated diagnosis of atopy to replicate these findings.

Supplementary Data

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.jana.2022.04.032>.

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Supplementary Data

eTable 1
ICD-9 Codes Pulled From the SPARCS

To identify asthma	To identify allergy(including food allergy)
493	693.1
493.0	692.5
493.00	558.3
493.01	477.1
493.02	995.6
493.1	995.60
493.10	995.61
493.11	995.62
493.12	995.63
493.2	995.64
493.20	995.65
493.21	995.66
493.22	995.67
493.8	995.68
493.81	995.69
493.82	995.7
493.9	477
493.90	477.0
493.91	477.2
493.92	477.8
	477.9

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; SPARCS, Statewide Planning and Research Cooperative System.

eTable 2
Associations of Maternal Gestational Weight Gain and Asthma and Other Atopic Outcomes in Singletons, Upstate KIDS Study, United States (2008–2019)

Outcome	N (%)		RR (95% CI)		N (%)	RR (95% CI)	
	Adequate (ref)	Inadequate	Unadjusted	Adjusted		Unadjusted	Adjusted
Early childhood (4–36 mo)							
Persistent wheeze	109 (10.41)	62 (11.05)	1.08 (0.76–1.53)	0.98 (0.69–1.40)	178 (10.68)	0.98 (0.74–1.28)	0.92 (0.70–1.21)
Any atopy	508 (41.71)	275 (41.60)	0.92 (0.79–1.06)	0.97 (0.84–1.12)	815 (42.14)	1.02 (0.92–1.14)	1.08 (0.97–1.20)
Eczema or atopic dermatitis	399 (32.76)	190 (28.74)	0.79 (0.65–0.95)	0.84 (0.70–1.02)	560 (28.96)	0.9 (0.79–1.02)	0.95 (0.84–1.09)
Food allergies	125 (11.72)	58 (10.12)	0.62 (0.41–0.93)	0.63 (0.42–0.95)	203 (12.01)	1.02 (0.79–1.32)	1.06 (0.82–1.38)
Middle childhood (7–9 y)							
Asthma (report + meds)	67 (14.79)	47 (19.11)	1.38 (0.90–2.11)	1.25 (0.81–1.93)	128 (18.00)	1.13 (0.81–1.58)	1.00 (0.72–1.4)
Eczema/atopic dermatitis	63 (14.03)	24 (9.80)	0.76 (0.42–1.39)	0.75 (0.39–1.42)	73 (10.28)	0.88 (0.56–1.36)	0.83 (0.52–1.32)
Allergies							
Physician-diagnosed	57 (15.53)	30 (14.63)	1.35 (0.78–2.32)	1.29 (0.75–2.22)	114 (20.11)	1.54 (1.02–2.32)	1.43 (0.93–2.18)
Medications	69 (15.40)	38 (15.51)	1.06 (0.64–1.74)	0.93 (0.57–1.52)	110 (15.49)	1.13 (0.79–1.62)	1.02 (0.70–1.48)

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

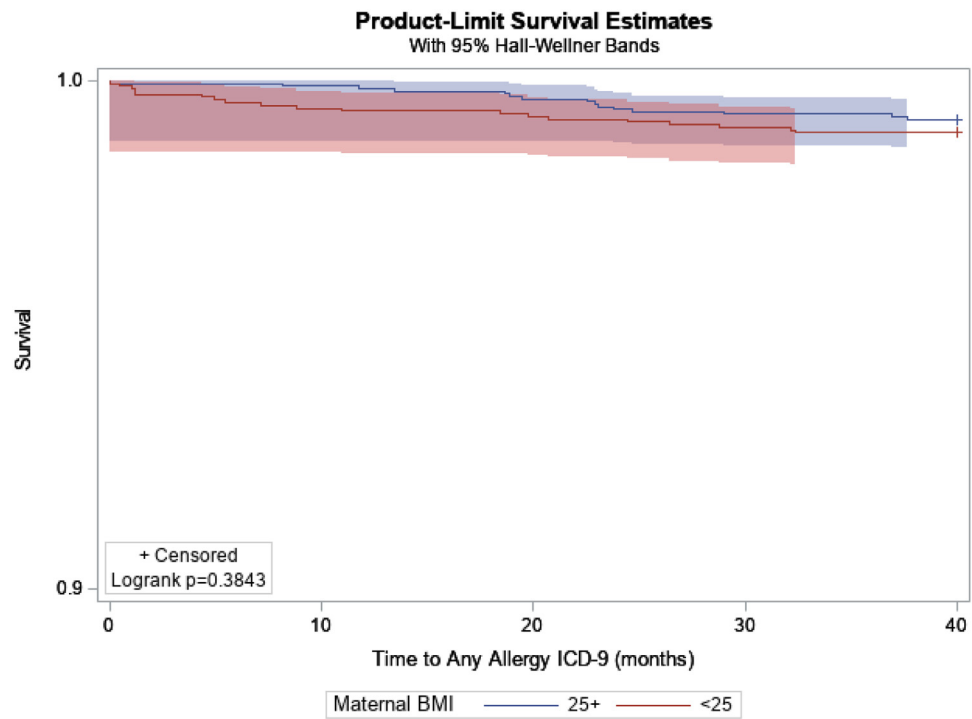
NOTE. Adjusted for maternal age, race/ethnicity, education, marital status, smoking, private insurance, maternal prepregnancy BMI, gestational age, and maternal atopy. Bold values indicate statistical significance.

eTable 3
Associations of Maternal Gestational Weight Gain and Asthma and Other Atopic Outcomes in Twins, Upstate KIDS Study, United States (2008–2019)

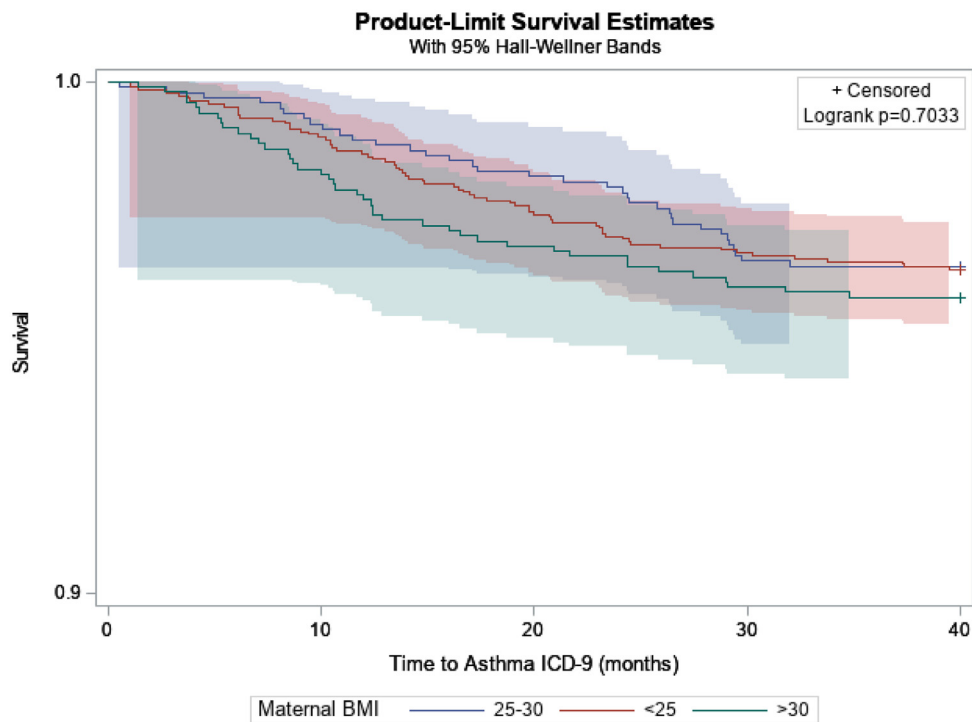
Outcome	N (%)		RR (95% CI)		N (%)	RR (95% CI)	
	Adequate (ref)	Inadequate	Unadjusted	Adjusted		Unadjusted	Adjusted
Early childhood (4–36 mo)							
Persistent wheeze	69 (9.07)	89 (14.10)	1.54 (1.05–2.25)	1.24 (0.83–1.84)	34 (10.56)	0.97 (0.61–1.55)	0.98 (0.62–1.56)
Any atopy	310 (33.62)	274 (35.45)	1.10 (0.93–1.31)	1.14 (0.96–1.35)	138 (34.24)	1.07 (0.86–1.34)	1.11 (0.90–1.37)
Eczema or atopic dermatitis	231 (25.05)	190 (24.58)	1.05 (0.85–1.3)	1.10 (0.88–1.36)	102 (25.31)	1.02 (0.80–1.31)	1.05 (0.83–1.34)
Food allergies	63 (8.08)	51 (7.82)	0.80 (0.51–1.23)	0.76 (0.49–1.19)	23 (6.87)	0.66 (0.38–1.14)	0.64 (0.37–1.09)
Middle childhood (7–9 y)							
Asthma (report + meds)	41 (12.97)	45 (20.45)	1.40 (1.00–1.96)	1.39 (0.78–2.49)	10 (9.62)	0.61 (0.31–1.21)	0.62 (0.31–1.24)
Eczema/atopic dermatitis	21 (6.67)	22 (10.05)	2.14 (0.70–6.52)	1.65 (0.81–3.37)	10 (9.71)	1.25 (0.25–6.29)	1.21 (0.50–2.94)
Allergies							
Physician-diagnosed	35 (13.78)	31 (17.03)	1.75 (0.24–12.96)	1.24 (0.61–2.53)	9 (11.39)	3.48 (0.50–24.07)	0.78 (0.34–1.81)
Medications	36 (11.50)	25 (11.36)	0.99 (0.70–1.4)	0.82 (0.38–1.77)	12 (11.76)	1.01 (0.45–2.26)	0.73 (0.30–1.80)

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

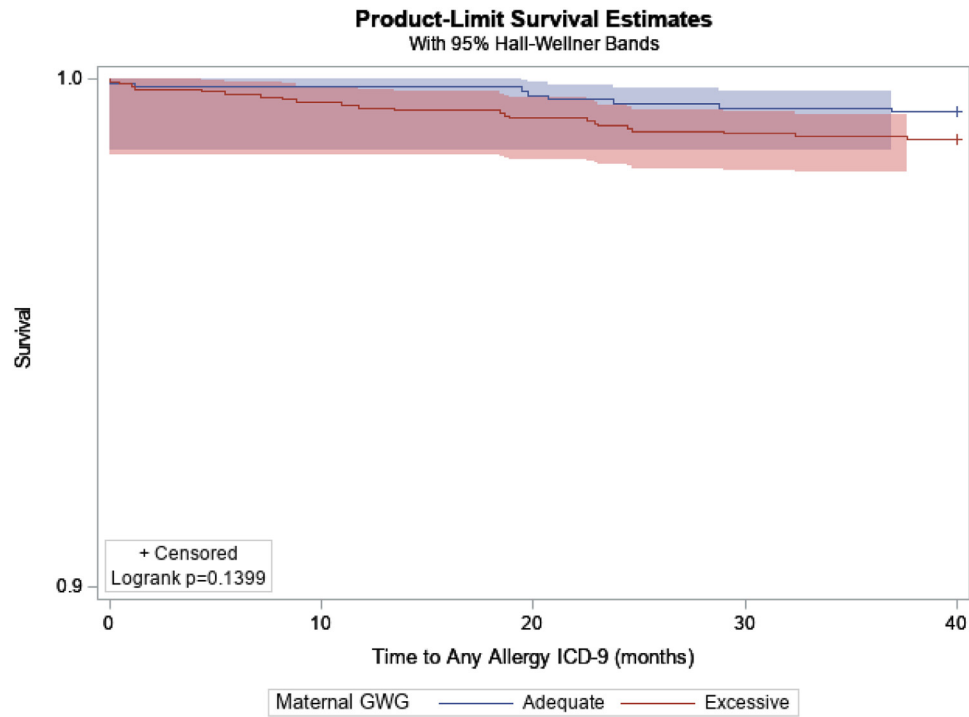
NOTE. Adjusted for maternal age, race/ethnicity, education, marital status, smoking, private insurance, maternal BMI, gestational age, and maternal atopy. Bold values indicate statistical significance.



eFigure 1. Kaplan-Meier plot for time to any allergy (mo) based on SPARCS stratified by maternal BMI. BMI, body mass index; ICD-9, International Classification of Diseases, Ninth Revision; SPARCS, Statewide Planning and Research Cooperative System.
Scale on y-axis modified to more clearly demonstrate the overlapping shaded confidence intervals.

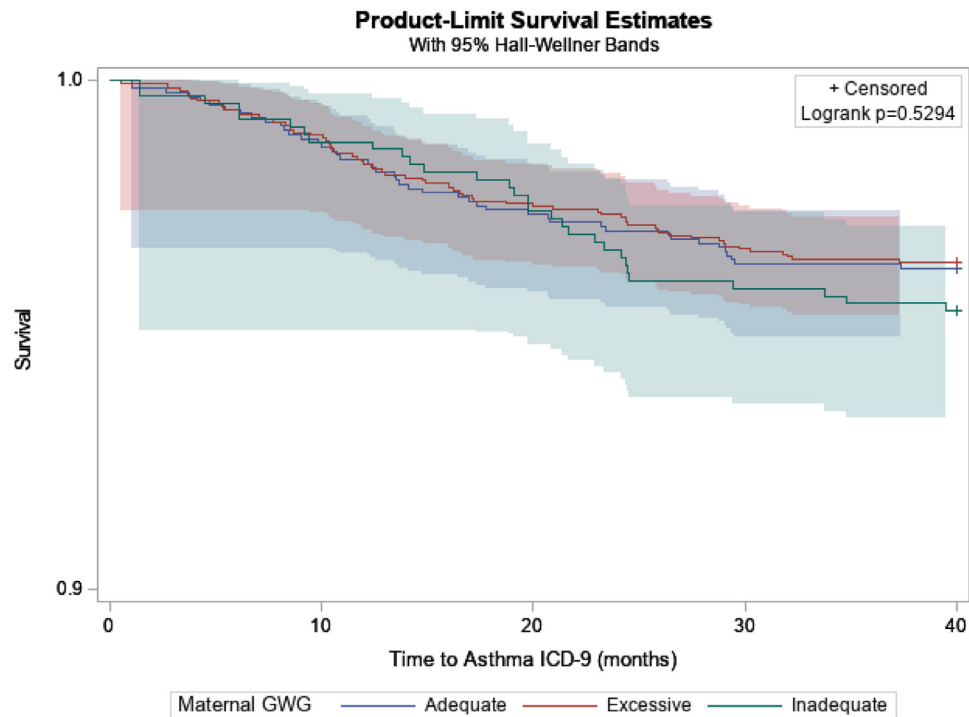


eFigure 2. Kaplan-Meier plot for time to asthma (mo) based on SPARCS stratified by maternal BMI categories. BMI, body mass index; ICD-9, International Classification of Diseases, Ninth Revision; SPARCS, Statewide Planning and Research Cooperative System.
Scale on y-axis modified to more clearly demonstrate the overlapping shaded confidence intervals.



eFigure 3. Kaplan-Meier plot for time to any allergy (mo) based on SPARCS stratified by maternal GWG. GWG, gestational weight gain; ICD-9, International Classification of Diseases, Ninth Revision; SPARCS, Statewide Planning and Research Cooperative System.

Scale on y-axis modified to more clearly demonstrate the overlapping shaded confidence intervals.



eFigure 4. Kaplan-Meier plot for time to asthma (months) based on SPARCS stratified by maternal GWG categories. GWG, gestational weight gain; ICD-9, International Classification of Diseases, Ninth Revision; SPARCS, Statewide Planning and Research Cooperative System.

Scale on y-axis modified to more clearly demonstrate the overlapping shaded confidence intervals.