

Prepregnancy body mass index and risk of childhood asthma

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Abstract

Background: Growing evidence suggests that maternal obesity may affect the intrauterine environment and increase a child's risk of developing asthma. We aim to investigate the relationship between prepregnancy obesity and childhood asthma risk.

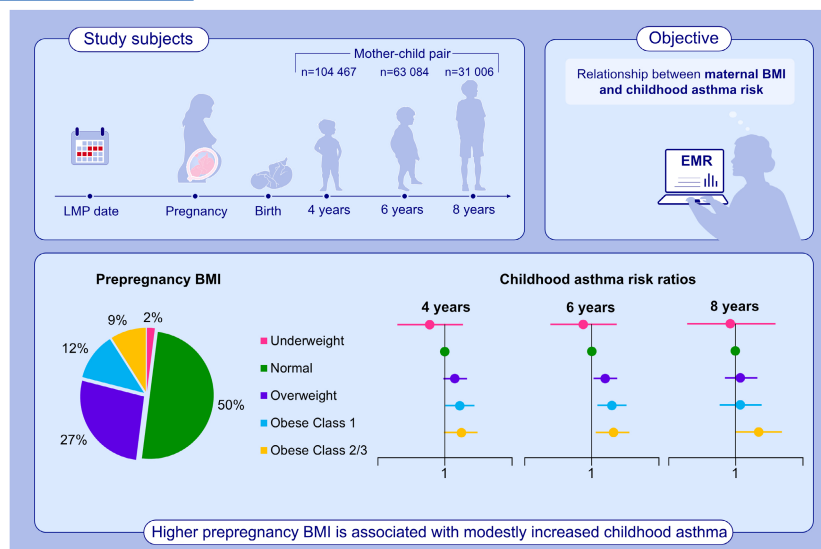
Methods: Cohorts of children enrolled in Kaiser Permanente Northern California integrated healthcare system were followed from birth (2005–2014) to age 4 ($n = 104,467$), 6 ($n = 63,084$), or 8 ($n = 31,006$) using electronic medical records. Child's asthma was defined using ICD codes and asthma-related prescription medication dispensing. Risk ratios (RR) and 95% confidence intervals (95% CIs) for child's asthma were estimated using Poisson regression with robust error variance for (1) prepregnancy BMI categories (underweight [<18.5], normal [18.5 – 24.9], overweight [25 – 29.9], obese 1 [30 – 34.9], and obese 2/3 [≥ 35]) and (2) continuous prepregnancy BMI modeled using cubic splines with knots at BMI category boundaries. Models were adjusted for maternal age, education, race, asthma, allergies, smoking, gestational weight gain, child's birth year, parity, infant sex, gestational age, and child's BMI.

Results: Relative to normal BMI, RRs (95% CIs) for asthma at ages 4, 6, and 8 were 0.91 (0.75, 1.11), 0.95 (0.78, 1.16), and 0.97 (0.75, 1.27) for underweight, 1.06 (0.99, 1.14), 1.08 (1.01, 1.16), and 1.03 (0.94, 1.14) for overweight, 1.09 (1.00, 1.19), 1.12 (1.03, 1.23), 1.03 (0.91, 1.17) for obese 1, and 1.10 (0.99, 1.21), 1.13 (1.02, 1.25), 1.14 (0.99, 1.31) for obese 2/3. When continuous prepregnancy BMI was modeled with splines, child's asthma risk generally increased linearly with increasing prepregnancy BMI.

Conclusions: Higher prepregnancy BMI is associated with modestly increased childhood asthma risk.

KEYWORDS

asthma, gestational weight gain, maternal obesity, pregnancy



GRAPHICAL ABSTRACT

This study investigated the relationship between maternal prepregnancy BMI and childhood asthma risk. Mothers were followed throughout their pregnancy, and children were followed up to age 4, 6, or 8 years using electronic medical records. Asthma was assessed at each follow-up age. Higher prepregnancy BMI was associated with a modest increase in childhood asthma risk. BMI, body mass index; EMR, electronic medical records; LMP, last menstrual period.

1 | INTRODUCTION

In 2019, the United States (US) Centers for Disease Control (CDC) reported that over 5.1 million children under the age of 18 years had asthma.¹ Close to half (2.3 million) were 5–11 years old.¹ Many studies have investigated risk factors for childhood asthma, including parental asthma, childhood overweight or obesity, and preterm birth.² The US has seen a relative increase of 11% in the prevalence of prepregnancy obesity from 2016–2019 (26.1% in 2016 to 29.0% in 2019).³ Many studies already suggest that maternal obesity increases the risk of childhood asthma,^{4,5} though the biological mechanisms are not clear. Prepregnancy obesity can impact the intrauterine environment thus affecting fetal development and the child's health later in life,^{6,7} specifically through inflammation pathways,⁷ which alter the microbiome of the fetus during important phases of immunological development.⁸

This study's objective is to investigate the relationship between maternal prepregnancy body mass index (BMI) and childhood asthma risk. We leverage electronic medical record (EMR) data from a large health maintenance organization to assess child outcomes 4–8 years after birth, an age when asthma diagnoses become more reliable.⁹ As the largest study to date in the US on this topic, the large number of mother–child pairs allowed for the assessment of obese subclasses, for which there is little data available to address the association with childhood asthma.

2 | METHODS

2.1 | Study population

The study population included mother–child pairs enrolled in the Kaiser Permanente Northern California (KPNC) integrated health

system while the mother was pregnant and gave birth between 1 January 2005 and 1 January 2014; follow-up was included through 1 January 2018. Singleton mother–child pairs were included providing the child had continuous enrollment through at least age 4, 6, or 8 years; children with a cystic fibrosis diagnosis were excluded from the initial cohort (because of unique patterns of medication use and impaired lung function, $n = 139$). Children were unenrolled when they left the KPNC system (e.g., changed insurance or lost insurance). A 90-day gap in enrollment was allowed as such short-term administrative gaps in enrollment can occur. The age 6 cohort was a subset of the age 4 cohort, and the age 8 cohort was a subset of the age 6 cohort (Figure 1). Decreased sample size by follow-up age was due to administrative censoring (i.e., not reaching follow-up age by January 1, 2018) or drop-out from the KPNC system (i.e., noncontinuous enrollment). Birth year was the major determinant of missing prepregnancy anthropometric measures (99% missing in 2005 decreasing to 12% missing in 2014) reflecting the incremental adoption of EMR across KPNC facilities over time. The remaining missingness was primarily due to women enrolling in KPNC mid-pregnancy (>10 weeks after last menstrual period [LMP]), which was about 6.3% of mothers. Exposure missingness was independent of all variables except birth year.

2.2 | Measures

2.2.1 | Exposure: Prepregnancy BMI

Pregpregnancy BMI was calculated using height and weight measurements from the mother's EMR data. The height measurement closest to the LMP date was used as the prepregnancy height. Prepregnancy weight was defined as the weight measurement closest to the LMP date but no more than 6 months prior or 10 weeks

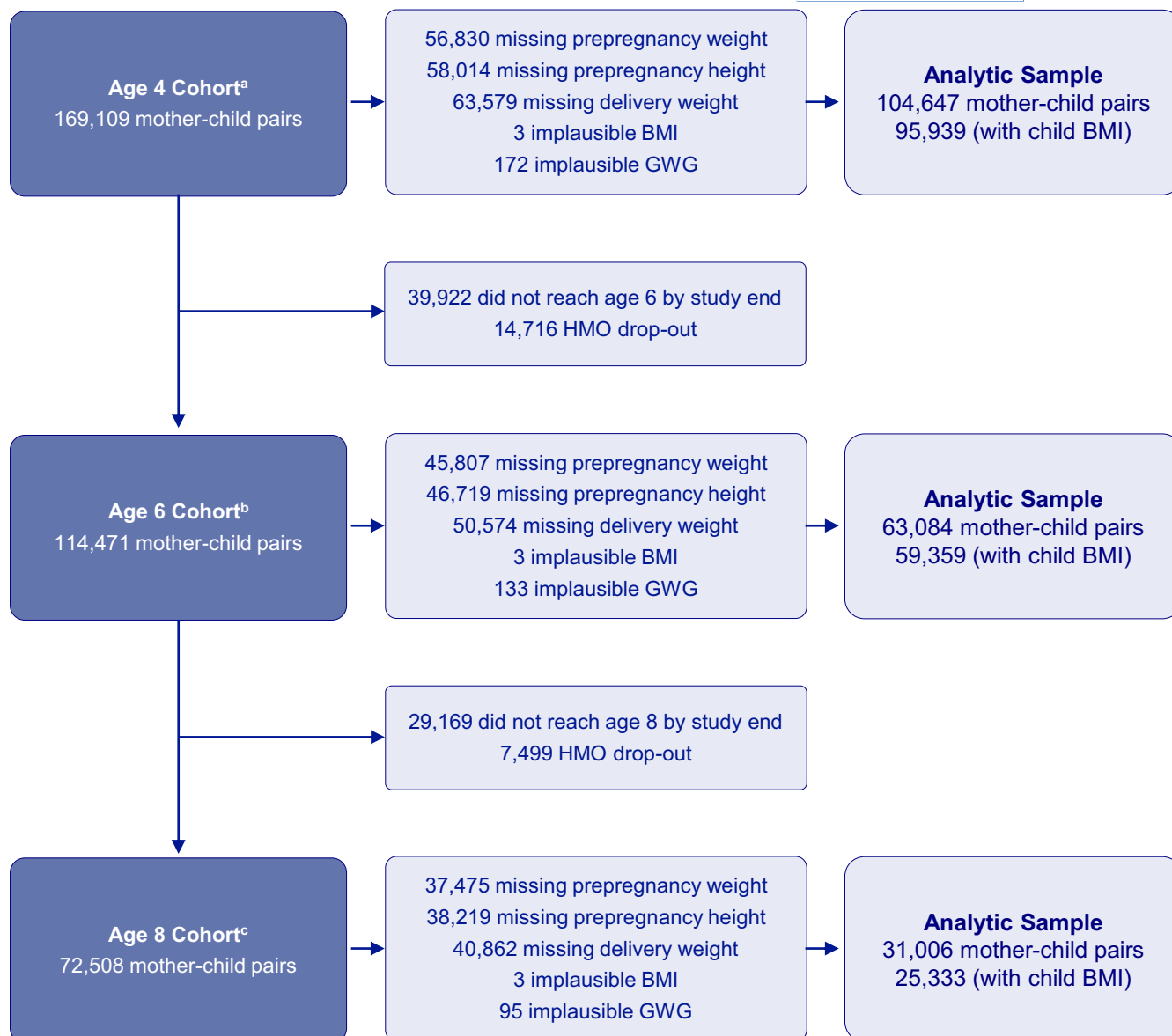


FIGURE 1 Follow-up flowchart. Some mother-child pairs were missing more than one measurement. BMI $<12 \text{ kg/m}^2$ or $>81 \text{ kg/m}^2$ and GWG $<-40 \text{ lbs}$ or $>100 \text{ lbs}$ were considered implausible. Most prepregnancy anthropometric measures were missing due to the incremental adoption of electronic medical records and women enrolling midpregnancy. Exposure (pregnancy BMI calculated from height and weight measurements) missingness was independent of all variables except birth year. BMI, body mass index; GWG, gestational weight gain; HMO, health maintenance organization. ^aCovers births from 1/1/2005 to 1/1/2014. ^bCovers births from 1/1/2005 to 1/1/2012. ^cCovers births from 1/1/2005 to 1/1/2010

after. Prepregnancy BMI was defined using CDC classification categories: underweight (BMI $<18.5 \text{ kg/m}^2$), normal (BMI $18.5\text{--}24.9 \text{ kg/m}^2$), overweight (BMI $25.0\text{--}29.9 \text{ kg/m}^2$), obese class 1 (BMI $30\text{--}34.9 \text{ kg/m}^2$), obese class 2 (BMI $35\text{--}39.9 \text{ kg/m}^2$), and obese class 3 (BMI 40+ kg/m^2).¹⁰ Obese class 2 and class 3 were combined due to small sample sizes in each category. Implausible prepregnancy BMI values (BMI <12 and BMI >81) were set to missing.

2.2.2 | Outcome: Child's asthma

Asthma was defined using a combination of International Classification of Disease (ICD) diagnosis codes and asthma-related

prescription medication dispensing. Two criteria were necessary for children to meet the primary asthma definition: (1) an inpatient discharge diagnosis code for asthma (with the primary code for asthma, or the second code for asthma and the primary code for acute respiratory infection) or two outpatient asthma ICD codes (ICD-9493 or ICD-10J45) at least 30 days apart and (2) two controller medication dispenses at least 30 days apart, with at least one within 12 months of the relevant follow-up age (4, 6, and 8 years); allowing a child's asthma status to change between follow-up ages.

The stringent primary asthma definition was designed to minimize false positives (prioritize high specificity) because (nondifferential) false negatives do not bias the risk ratio^{11(p359)} A secondary, less stringent definition was examined in sensitivity analyses, and

only required one controller medication dispensing in the child's history and either an asthma diagnosis or one controller medication dispensing in the past 12 months of each relevant follow-up age. All children who met the criteria for the primary definition also met the criteria for the secondary definition.

2.2.3 | Covariates

Maternal and child information was collected from EMR data in the KPNC system. Maternal characteristics included age, education, race and ethnicity, asthma, allergies, smoking during this pregnancy, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, cesarean delivery, and total GWG (implausible values [GWG < -40 lbs. and GWG > 100 lbs.] set to missing). Child characteristics were birth year, gestational age, infant sex, birth weight, parity, neonatal intensive care unit (NICU) admission, first-year antibiotics, and child's BMI. Details on covariate definitions are provided in the Supplement (S1).

2.3 | Statistical analysis

Using modified Poisson regression models with robust variance estimation^{12,13} we estimated risk ratios (RR) and 95% confidence intervals (CI) at each follow-up age. Prepregnancy BMI was modeled in two ways: first as a categorical variable (using categories previously described) and second as a continuous variable, using cubic splines with knots at BMI category boundaries allowing for a flexible non-linear relationship.^{14,15} Continuous total GWG was modeled flexibly using a cubic spline with knots on percentiles in the final adjusted model.

Covariates listed above were evaluated as potential confounding variables based on previous research^{14,16,17} and a priori directed acyclic graphs (DAGs). The DAG (created using DAGitty¹⁸) in Figure 2 shows an example of how some covariates could be considered both confounders (through backdoor pathways) and/or intermediates (on the pathway) between prepregnancy BMI and child's asthma (full DAG in Figure S1). For example, prepregnancy

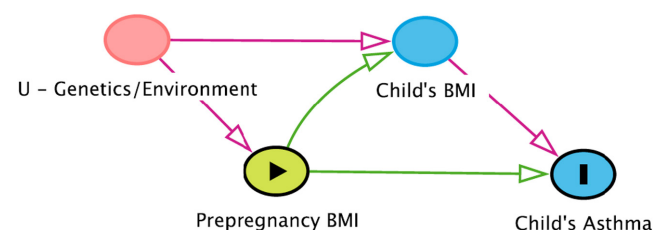


FIGURE 2 Directed acyclic graph of maternal prepregnancy BMI and child's asthma showing confounding and mediation pathways through child's BMI. Exposure = prepregnancy BMI. Outcome = child's asthma. Green arrow = causal pathway. Pink arrow = biasing pathway. BMI, body mass index

BMI and child's BMI are likely affected by unmeasured common causes such as genetics or environmental factors. Though child's BMI could also be on the causal pathway between prepregnancy BMI and child's asthma. There were several other variables that could have a similar structure in Figure 2, replacing the child's BMI. These included: GWG, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, cesarean section, gestational age, birth weight, NICU admission, and child's first-year antibiotics. Analyses were conducted to assess how each of these individual covariates affected prepregnancy BMI RRs.

An analysis focused on incident asthma cases was also performed for comparison. In this analysis, children who received a previous asthma diagnosis were excluded from later follow-up age analyses (e.g., children who received an asthma diagnosis at age 4 were not included in the age 6 cohort analysis). Additionally, children who received an asthma diagnosis at each follow-up age were analyzed in similar models. In the literature, GWG is inconsistently operationalized and there is debate on which method is most informative.¹⁹ Additional sensitivity analyses were conducted operationalizing GWG differently (Table S3; S5.2).

Study protocols were approved by the University of Nevada, Reno, and KPNC Institutional Review Boards (IRB). All KPNC members provided consent to medical research using their EMR data upon enrollment. The reporting guideline checklist for observational research using routinely collected data (RECORD)²⁰ was completed for this study (S1). All analyses were completed in SAS 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Among children in the age 4, 6, and 8 cohorts, 5.0%, 7.5%, and 8.1%, respectively, met the primary asthma definition (Table 1; secondary asthma definition in Table S1). Across cohorts, half of the mothers had a normal prepregnancy BMI, 2% had an underweight prepregnancy BMI, 27% had an overweight prepregnancy BMI, 12% had an obese class 1 prepregnancy BMI, and 9% had an obese class 2/3 prepregnancy BMI (Tables 2 and S2). Tables 1 and 2 show the strongest predictors of childhood asthma among child characteristics were infant sex (male), birth weight (<2500g), NICU admission, first-year antibiotics, and child's obesity (BMI > 95th percentile), and among maternal characteristics were prepregnancy obesity (class 1, and 2/3), race (Black), active asthma, allergies, diabetes (pregnancy and gestational), hypertension (chronic and gestational), prenatal antibiotics, and cesarean section.

In unadjusted models (shown in Figure S2), RRs in the age 4 cohort were 0.91 (95% CI: 0.75, 1.10) for underweight, 1.16 (95% CI: 1.09, 1.24) for overweight, 1.28 (95% CI: 1.18, 1.39) for obese class 1, and 1.44 (95% CI: 1.31, 1.57) for obese class 2/3 relative to normal prepregnancy BMI. Among children in the age 6 cohort, unadjusted RRs were 0.98 (95% CI: 0.80, 1.19) for underweight, 1.19 (95% CI: 1.11, 1.27) for overweight, 1.32 (95% CI: 1.21, 1.44) for obese class

TABLE 1 Child characteristics for follow-up ages 4, 6, and 8

	Asthma age 4	Total age 4	Asthma age 6	Total age 6	Asthma age 8	Total age 8
	N (%)	N	N (%)	N	N (%)	N
Total	5251 (5.0)	104,467	4729 (7.5)	63,084	2518 (8.1)	31,006
Infant sex						
Male	3352 (6.3)	53,309	2975 (9.2)	32,178	1566 (9.9)	15,881
Female	1899 (3.7)	51,158	1754 (5.7)	30,906	952 (6.3)	15,125
Birth weight						
<2500g	390 (8.8)	4440	327 (12.5)	2612	162 (13.0)	1246
2500–4000g	4284 (4.9)	88,055	3866 (7.3)	53,175	2061 (7.9)	26,016
>4000g	577 (4.8)	11,972	536 (7.3)	7297	295 (7.9)	3744
Parity						
First born	2187 (4.9)	45,034	1999 (7.4)	26,938	1062 (8.1)	13,040
Second born	2020 (5.3)	38,092	1788 (7.7)	23,081	945 (8.3)	11,388
Third born +	1044 (4.9)	21,341	942 (7.2)	13,065	511 (7.8)	6578
NICU admission						
Yes	585 (8.4)	6937	513 (12.0)	4260	266 (12.5)	2127
No	4666 (4.8)	97,530	4216 (7.2)	58,824	2252 (7.8)	28,879
First-year antibiotics						
Yes	3199 (8.1)	39,719	2706 (10.7)	25,194	1435 (11.1)	12,898
No	2052 (3.2)	64,748	2023 (5.3)	37,890	1083 (6.0)	18,108
Child BMI ^a (pct)						
Underweight (<5th)	248 (5.3)	4698	174 (7.4)	2339	78 (8.3)	941
Normal (5th–84th)	3434 (5.0)	69,169	2936 (7.1)	41,353	1508 (8.5)	17,676
Overweight (85th–95th)	828 (5.9)	13,975	810 (8.5)	9523	384 (10.3)	3746
Obese (>95th)	647 (7.2)	9036	759 (11.4)	6650	427 (13.5)	3169
Missing	94 (1.2)	7589	50 (1.6)	3219	121 (2.2)	5474
Gestational age (weeks)						
Mean [SD]	38.4 [2.2]	38.9 [1.7]	38.5 [2.1]	38.9 [1.7]	38.6 [2.0]	38.9 [1.7]

Abbreviations: BMI, body mass index; NICU, neonatal intensive care unit.

^aChild BMI percentiles calculated using height and weight measurements within 6 months of previous birthday.

1, and 1.49 (95% CI: 1.36, 1.64) for obese class 2/3 relative to normal. And among children in the age 8 cohort, unadjusted RRs were 0.96 (95% CI: 0.74, 1.24) for underweight, 1.15 (95% CI: 1.05, 1.26) for overweight, 1.24 (95% CI: 1.11, 1.40) for obese class 1, and 1.50 (95% CI: 1.33, 1.70) for obese class 2/3 relative to normal.

Adjusted models included potential confounding variables based on previous research^{14,16,17} and a priori DAGs. In all models, these covariates included maternal characteristics: age, education, race and ethnicity, asthma, allergies, smoking; and child characteristics: birth year, parity, and infant sex. Of these covariates, maternal education, race/ethnicity, asthma, and allergies had the strongest effect on prepregnancy BMI estimates. Other covariates were evaluated individually to assess their effect on prepregnancy BMI estimates due to potential roles as both intermediates and confounders (listed above). GWG and gestational age had small impacts on prepregnancy BMI estimates but did not meaningfully change overall conclusions. Child's BMI had a larger impact on prepregnancy BMI estimates, substantially decreasing the magnitude of the association

when included in models. Ultimately, GWG, gestational age, and child's BMI were also included in the final adjusted models (results excluding these covariates from models presented in Figures S2 and S5.3). GWG was operationalized in several different ways, though each method showed similar results for prepregnancy BMI estimates (Table S3).

Adjusted RRs and 95% CI by prepregnancy BMI categories for each cohort are presented in Figure 3. Results show elevated RRs for prepregnancy BMI categories overweight, obese class 1, and obese class 2/3, relative to normal prepregnancy BMI, though adjusted RRs are closer to 1.00 than the unadjusted RRs. This pattern is consistent across cohorts, though strongest among the age 6 cohort. Using the secondary asthma definition, RRs for the age 4 and age 6 cohorts were more precise (due to larger number of asthma cases) showing similar patterns compared with the primary asthma definition (Figure S3). Additionally, RRs for the age 8 cohort were slightly higher for prepregnancy BMI categories overweight, obese class 1, and obese class 2/3. In the incident asthma cases analysis, results

TABLE 2 Maternal characteristics for follow-up ages 4, 6, and 8

	Asthma age 4	Total age 4	Asthma age 6	Total age 6	Asthma age 8	Total age 8
	N (%)	N	N (%)	N	N (%)	N
Total	5251 (5.0)	104,467	4729 (7.5)	63,084	2518 (8.1)	31,006
Prepregnancy BMI ^a						
Underweight	104 (4.1)	2528	97 (6.5)	1500	54 (7.0)	771
Normal	2339 (4.5)	51,845	2078 (6.6)	31,402	1130 (7.3)	15,427
Overweight	1476 (5.2)	28,153	1329 (7.9)	16,896	695 (8.4)	8266
Obese 1	747 (5.8)	12,902	684 (8.7)	7821	348 (9.0)	3870
Obese 2 and 3	585 (6.5)	9039	541 (9.9)	5465	291 (10.9)	2672
Mean [SD]	27.0 [6.3]	26.2 [5.9]	27.0 [6.3]	26.1 [5.9]	27.0 [6.3]	26.1 [5.9]
Age (years)						
Mean [SD]	31.1 [5.3]	31.3 [5.1]	31.2 [5.3]	31.3 [5.1]	31.2 [5.4]	31.2 [5.1]
Education (years)						
<12	197 (5.4)	3660	204 (8.7)	2333	116 (9.4)	1240
12–15	2366 (5.5)	43,201	2246 (8.4)	26,723	1240 (9.1)	13,625
16+	2611 (4.6)	56,571	2225 (6.6)	33,477	1138 (7.2)	15,910
Missing	77 (7.4)	1035	54 (9.8)	551	24 (10.4)	231
Race/Ethnicity						
White	1868 (4.1)	45,446	1629 (6.0)	27,372	865 (6.4)	13,519
Black	498 (8.4)	5923	422 (11.7)	3611	245 (13.3)	1841
API	1492 (5.1)	29,274	1394 (8.0)	17,532	713 (8.4)	8501
Hispanic	1352 (5.8)	23,133	1258 (8.9)	14,192	691 (9.9)	7000
Other/Missing	41 (5.9)	691	26 (6.9)	377	4 (2.8)	145
Asthma ^b						
Active	1186 (9.0)	13,246	1075 (14.0)	7690	538 (15.0)	3590
Past	463 (6.7)	6893	436 (10.3)	4240	240 (10.8)	2226
None	3602 (4.3)	84,328	3218 (6.3)	51,154	1740 (6.9)	25,190
Allergies ^c						
Yes	3190 (6.1)	52,237	2995 (9.1)	32,852	1641 (9.8)	16,720
No	2061 (3.9)	52,230	1734 (5.7)	30,232	877 (6.1)	14,286
Smoking during pregnancy						
Yes	521 (5.4)	9573	430 (8.0)	5404	213 (8.6)	2491
No	4730 (5.0)	94,894	4299 (7.5)	57,680	2305 (8.1)	28,515
Prepregnancy diabetes						
Yes	153 (7.1)	2167	137 (10.2)	1337	81 (11.8)	688
No	5098 (5.0)	102,300	4592 (7.4)	61,747	2437 (8.0)	30,318
Gestational diabetes						
Yes	742 (5.4)	13,832	672 (8.2)	8197	350 (9.6)	3648
No	4509 (5.0)	90,635	4057 (7.4)	54,887	2168 (7.9)	27,358
Chronic hypertension						
Yes	241 (6.4)	3754	246 (9.8)	2498	138 (10.9)	1270
No	5010 (5.0)	100,713	4483 (7.4)	60,586	2380 (8.0)	29,736
Gestational hypertension						
Yes	722 (6.0)	11,961	639 (8.9)	7220	336 (10.0)	3370
No	4529 (4.9)	92,506	4090 (7.3)	55,864	2182 (7.9)	27,636

TABLE 2 (Continued)

	Asthma age 4	Total age 4	Asthma age 6	Total age 6	Asthma age 8	Total age 8
	N (%)	N	N (%)	N	N (%)	N
Breastfeeding						
<3 months	1375 (5.6)	24,457	1180 (7.7)	15,297	647 (8.5)	7625
3–6 months	847 (5.8)	14,660	760 (8.3)	9126	379 (8.7)	4351
>6 months	2576 (4.5)	57,576	2369 (7.0)	33,770	1248 (7.6)	16,414
None	441 (5.9)	7513	411 (8.7)	4738	240 (9.5)	2524
Missing	12 (4.6)	261	9 (5.9)	153	4 (4.3)	92
Prenatal antibiotics						
Yes	1872 (6.2)	29,991	1681 (9.1)	18,407	922 (10.1)	9158
No	3379 (4.5)	74,476	3048 (6.8)	44,677	1596 (7.3)	21,848
Cesarean section						
Yes	1633 (5.8)	27,971	1499 (8.8)	17,016	810 (9.6)	8414
No	3618 (4.7)	76,496	3230 (7.0)	46,068	1708 (7.6)	22,592
Total GWG ^d						
Inadequate	1120 (5.2)	21,520	921 (7.3)	12,652	486 (7.9)	6147
Adequate	1630 (4.8)	34,164	1486 (7.2)	20,748	788 (7.7)	10,186
Excessive	2501 (2.1)	48,783	2322 (7.8)	29,684	1244 (8.5)	14,673
Mean [SD]	29.1 [14.2]	29.7 [13.7]	29.4 [14.0]	29.9 [13.6]	29.9 [14.4]	30.0 [13.7]

Abbreviations: BMI, body mass index; GWG, gestational weight gain.

^aPrepregnancy BMI categories: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese class 1 (30–34.9 kg/m²), obese class 2/3 (35+ kg/m²).

^bAsthma during this pregnancy determined using diagnoses reported on medical intake forms and medication dispensing.

^cMaternal allergies including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the electronic medical record.

^dCalculated as delivery weight minus prepregnancy weight; based on the Institutes of Medicine recommended weight gain per prepregnancy BMI category.

were similar to those reported above (Table S4). Additionally, results from models including children who received an asthma diagnosis at each follow-up age were largely compatible with the main analysis but had less precision (Table S4).

The results from adjusted models including continuous prepregnancy BMI cubic splines are shown in Figure 4; RRs are presented relative to a reference of BMI = 22 kg/m² (i.e., RR = 1 at BMI = 22 kg/m²). Among children in the age 4 cohort, there was a general trend of increasing asthma risk as prepregnancy BMI increased from 18–30 kg/m². In the age 6 cohort asthma risk increased as prepregnancy BMI increased from BMI values of 20–35 kg/m², then decreased slightly, though confidence intervals widened. The age 8 cohort asthma risk generally increased as prepregnancy BMI increased. These patterns were similar for both the primary and secondary asthma definitions among all cohorts (Figure S4).

4 | DISCUSSION

In this study of over 100,000 mother–child pairs followed for at least 4 years after birth, the risk of childhood asthma increased as prepregnancy BMI increased. This increased risk was observed using two asthma definitions, three follow-up cohorts (4, 6, and 8 years),

and with prepregnancy BMI operationalized as both categorical and continuous variables. Though some estimates were nonsignificant, RRs for prepregnancy BMI categories were similar in magnitude and direction across each cohort and both asthma definitions. The RRs for higher prepregnancy BMI categories (overweight, obese class 1, and obese class 2/3) were highly attenuated after adjustment of important confounders including child's BMI but still indicated 2–14% increases in risk for these prepregnancy BMI categories relative to normal BMI.

Other studies also report positive associations between maternal obesity and childhood risk of asthma in similar age groups,^{5,14–17,21–28} though others have reported an inverse association²⁹ or no association.^{30,31} A recent meta-analysis found that maternal prepregnancy overweight or obesity significantly increased the odds of childhood asthma (OR = 1.41, 95% CI = 1.26, 1.59) as did a one unit (kg/m²) increase in prepregnancy BMI (OR = 1.03, 95% CI = 1.02, 1.03).⁵ Compared with these previous studies, our results are in the same direction (showing a positive association between prepregnancy BMI and childhood asthma) but are smaller in magnitude. There may be several reasons for this. Many previous studies did not include newer subcategories of obesity (i.e., obese class 1, 2, and 3),^{14,16,17,21,23–30} nor did they have large sample sizes.^{16,21,24,26,28–31} Previous studies also mainly relied on self-reported

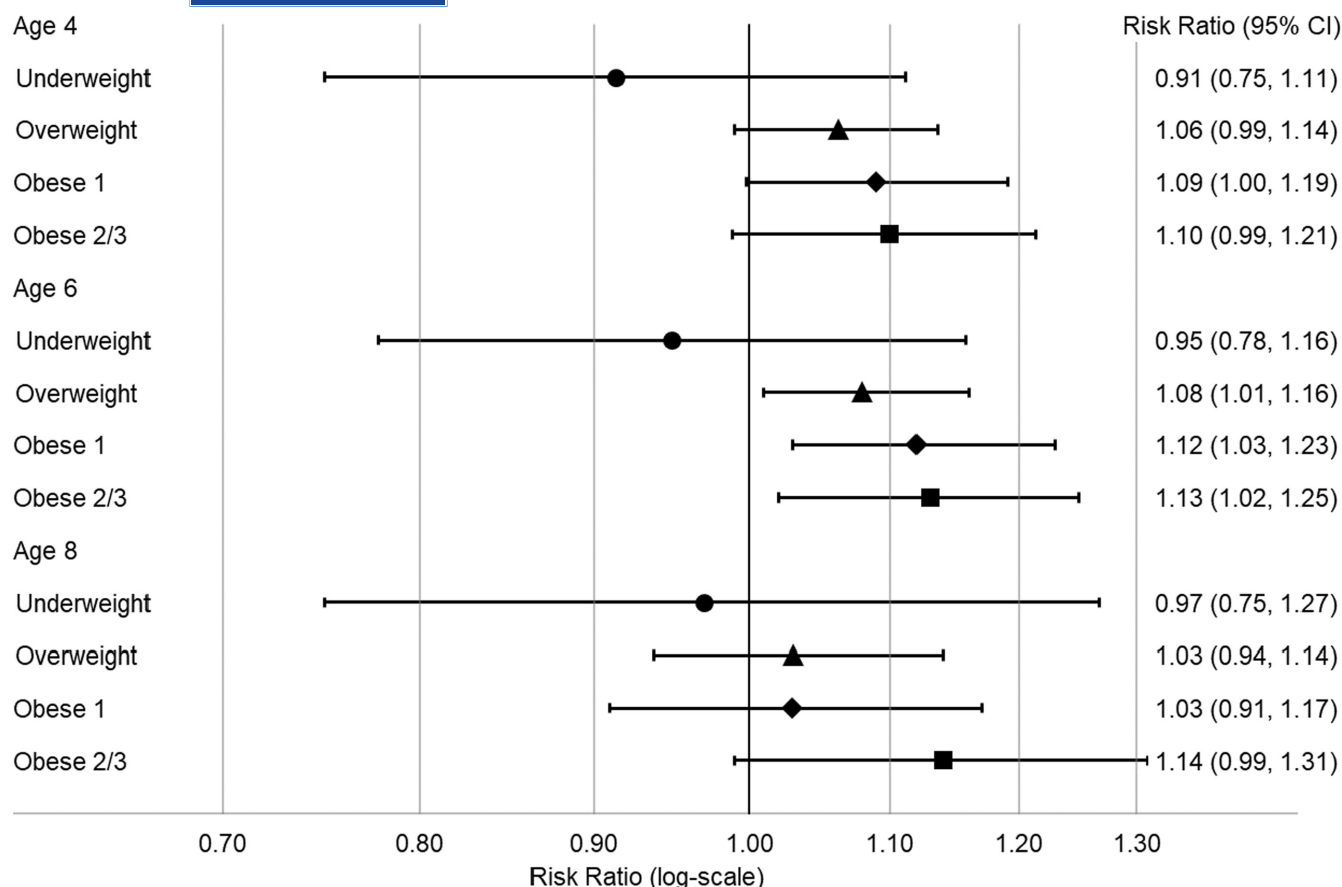


FIGURE 3 Adjusted risk ratios for prepregnancy BMI category (relative to Normal) and child's asthma, for follow-up ages 4, 6, and 8. Prepregnancy BMI categories: underweight (BMI <18.5 kg/m²), normal (BMI 18.5–24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m²), obese class 1 (BMI 30–34.9 kg/m²), obese class 2/3 (BMI ≥35). All models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI. BMI, body mass index

data^{14,16,21,24,26,28–31} and did not consider a large number of potential confounding variables,^{14,21,22,25–27,29–31} which could cause residual confounding. In particular, previously published studies have largely ignored possible influences of GWG,^{15,16,21,24,25,27,28} gestational age,^{14,21,22,24,25,27,28,30} and child's BMI^{5,14,15,17,22,25,26,28–31} on the relationship between prepregnancy BMI and child's asthma risk.

Although the literature shows a link between prepregnancy obesity and child's asthma development, there are no clear biological mechanisms. One possibility is through inflammatory pathways. Prepregnancy obesity is associated with chronic inflammation, elevated levels of inflammatory cytokines, and changes to inflammatory and metabolic markers, which during pregnancy are associated with child's asthma development.³² This chronic inflammation in pregnancy can alter the mother's microbiome and subsequently the microbiome of the fetus.⁷ Alterations in the microbiome of the lungs and/or intestines and circulating maternal inflammatory markers can shape early immunological development, thus contributing to immune deficiencies associated with asthma development.^{7,8} Shared genetic factors related to obesity, epigenetic imprinting, fetal programming, and shared environmental factors (e.g., diet and physical activity habits) can also play a role.^{7,32}

This study included many covariates, in both the mother's and child's EMR data. According to a priori DAGs, some of these

covariates could act as confounders or intermediates on the estimated association between prepregnancy BMI and child's asthma. Each of these covariates (GWG, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, cesarean section, gestational age, birth weight, NICU admission, child's first-year antibiotics, and child's BMI) were evaluated individually, and only three (GWG, gestational age, and child's BMI) had any effect on the estimated associations between prepregnancy BMI and child's asthma beyond the base set of likely confounders included in all models (maternal age, education, race and ethnicity, asthma, allergies, smoking; and child's birth year, parity, and infant sex; additional discussion in S1.3).

GWG and gestational age had small impacts on prepregnancy BMI estimates but did not meaningfully change conclusions. It is well established GWG and gestational age are affected by prepregnancy obesity and it is possible that these factors are on the causal pathway between prepregnancy BMI and childhood asthma.^{33,34} It is also possible common causes of prepregnancy obesity and GWG (e.g., maternal age and smoking) and prepregnancy obesity and gestational age (e.g., socioeconomic status) heavily confound the association between prepregnancy BMI and child's asthma.^{4,7} Several other studies have adjusted for GWG and gestational age, though none have included formal mediation analyses.^{5,14–17,26,29–31}

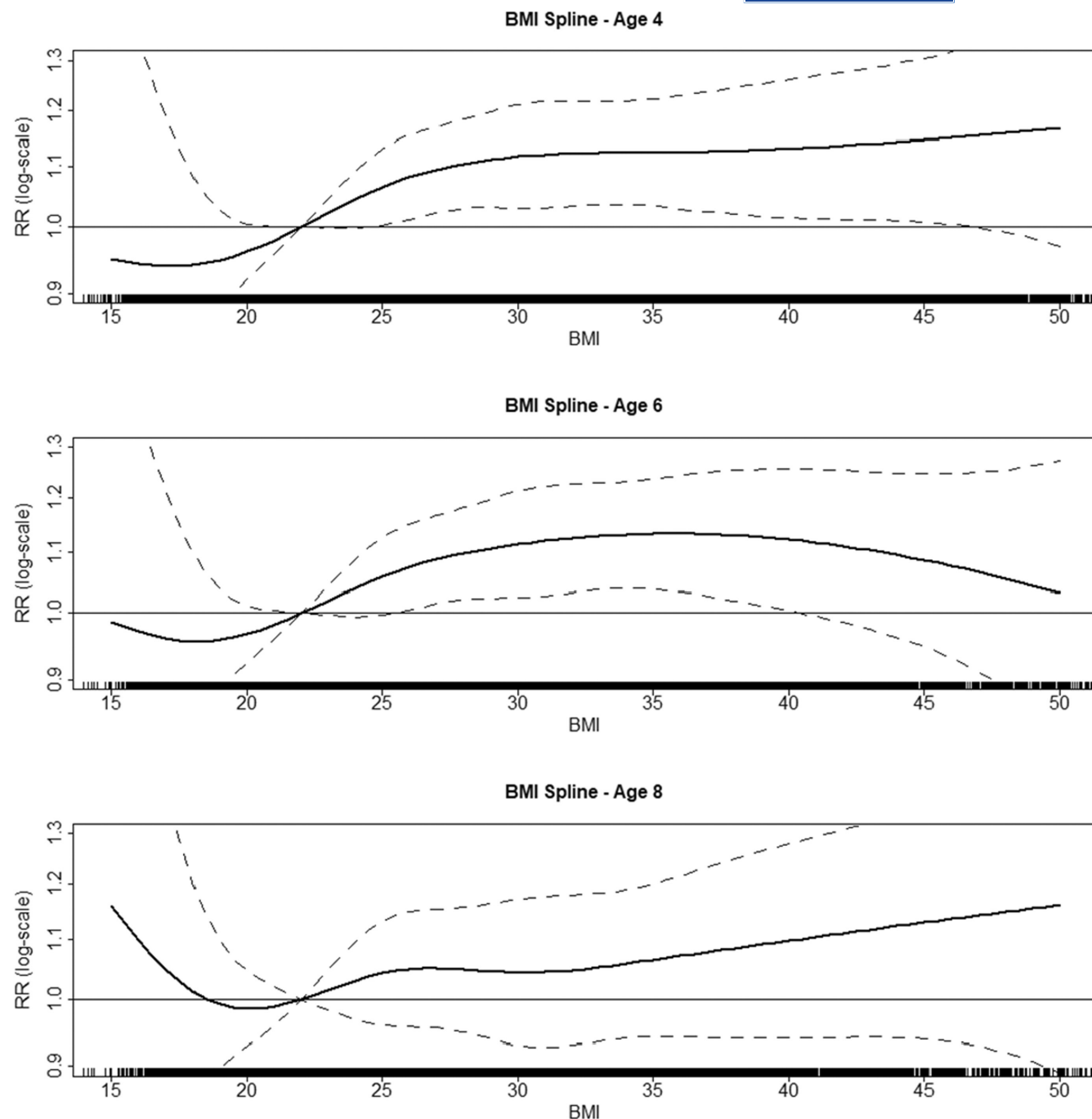


FIGURE 4 Adjusted risk ratios for continuous BMI (spline) and child's asthma, for follow-up ages 4, 6, and 8. All models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI. Risk ratios are presented relative to a reference of BMI = 22 kg/m². Rug is presented along the x-axis of each graph to show the distribution of data. BMI, body mass index; RR, risk ratio

Inclusion of child's BMI (measured closest to the child's last birthday) in the models meaningfully changed prepregnancy BMI estimates; observed associations were stronger when child's BMI was not included in the models. Childhood obesity is a known risk factor for childhood asthma.³⁵ There is also evidence linking prepregnancy obesity and child's BMI, through direct pathways like in-utero epigenetic processes that directly contribute to childhood obesity,³⁶ and/or confounding pathways with common causes such as genetics, lifestyle factors, and nutrition.³⁷ It is possible that the link

between prepregnancy obesity and child's BMI is a complex combination of these pathways.³⁷ One previous study included child's BMI as a confounder in their analysis of prepregnancy BMI and child's asthma,²⁴ while two others found attenuating effects and concluded that child's BMI may partly mediate the effect of maternal obesity on childhood asthma.^{22,27} Though, more formal mediation analyses have found weak evidence²¹ and no evidence at all.¹⁶

There are many strengths in this study. The data source relied on EMR data, not self-reported data. In addition to being less susceptible

to recall bias, the EMR data for both mothers and children included many covariates that were important for this analysis. EMR data also included prospectively collected serial measurements on mother's height and weight, child's height and weight, and breastfeeding; and routinely collected objective diagnostic data and medication dispensing. Additionally, using EMR data ensured the accuracy of events at birth (delivery method and birth weight), and allowed for the collection of many confounding factors such as maternal characteristics (i.e., age, race/ethnicity, education, etc...), maternal conditions (i.e., asthma, allergies, diabetes, etc.), and child characteristics (i.e., NICU admission, first-year antibiotics, and child's BMI). This study included a large number of mother-child pairs for analysis, even at subsequent follow-up ages and for maternal obesity subclasses, making it the largest study to date on this topic in the US. Asthma outcome status was determined using a combination of ICD codes and prescription dispensing. The primary asthma definition was designed to minimize false positives (to avoid bias in the risk ratio due to outcome measurement error^{11(p359)}) and we also conducted sensitivity analyses using a secondary, less stringent asthma definition that yielded the same conclusions. Asthma was also assessed at multiple follow-up ages when asthma diagnoses are more reliable.⁹ More specific categories of prepregnancy BMI were included (i.e., obese class 1, 2, and 3) and prepregnancy BMI was modeled in two ways (categorically and continuously). And finally, important variables often absent in the previous literature were included and assessed in this study.

This study is not without limitations. It is possible some covariates, specifically GWG, gestational age, and child's BMI, included in final adjusted models were on the pathway from prepregnancy BMI and childhood asthma. If this is the case, our estimated associations can be interpreted as the effect of prepregnancy BMI on childhood asthma apart from any effect through GWG, gestational age, and child's BMI. However, as discussed above, evidence for confounding pathways was more evident in the literature than evidence for mediating pathways for these covariates. Hence, the final models adjusted for these covariates (results without adjusting for these covariates are presented in Figures S2 and S5.3). It is also possible, that while many confounding variables were considered and adjusted for, residual confounding, due to unmeasured or poorly measured factors (such as genetics, socioeconomic status, lifestyle factors, or environment—all strong determinants of maternal and childhood obesity) may be present. Weight measurements up to 10 weeks into pregnancy were used for prepregnancy BMI calculations (for some women); it is possible that those women had already started to gain weight, which may lead to exposure misclassification. Though, weight gain in the first trimester is known to be small (typically between 1 and 4 lbs.),³⁸ and in our study population average weight by gestational week did not start increasing until the second trimester (Figure S5). The use of EMR data and algorithms to determine outcome status may have led to misclassification of the outcome; however, the magnitude of the bias in the risk ratio would be entirely driven by the number of false positives,^{11(p359)} which motivated our primary asthma definition requiring multiple diagnoses and medications. Our secondary asthma definition yielded similar results. The comprehensive diagnosis and medication histories available on the study population are a strength of this study

but represent a fully-insured cohort that may not be generalizable to other populations. Additionally, selection bias may also occur from many mother-child pairs being excluded due to missing exposure data (pregnancy BMI calculated from height and weight measurements); however, missing exposure was unrelated to any study variables except birth year reflecting the increasing use of EMR over time.

These findings suggest higher prepregnancy BMI is modestly associated with childhood asthma risk. This relationship holds after controlling for important maternal characteristics, maternal asthma and allergies, GWG, gestational age, and child's BMI. Given the increasing prevalence of both prepregnancy obesity³ and childhood asthma,⁹ it is important to consider a possible causal link between the two. This could lead to further exploration of potential mechanisms and preventative interventions. Such interventions would not only benefit women throughout their pregnancy but would also have positive impacts on reducing the risk of childhood asthma.

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AUTHOR CONTRIBUTIONS

NAR, JRF, DKL, and LAD designed the study with input from MR, SYR, HB, and MJS. JRF and DKL extracted and reviewed electronic medical record data. NAR, MR, JRF, and LAD conducted the analyses, and NAR, MR, and LAD reviewed and interpreted the results. NAR wrote the manuscript, which was reviewed and approved by the rest of the authors.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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