University of Nevada, Reno

Prepregnancy Body Mass Index, Gestational Weight Gain,

and Child's Asthma Development

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By

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Abstract

The prevalence of childhood asthma, maternal prepregnancy obesity, and excessive gestational weight gain (GWG) have been on the rise in recent decades. This has brought attention to these topics and whether maternal weight related metrics affect the risk of asthma. Methodological challenges and data quality have led to mixed results presented in the literature. This dissertation aims to further investigate the association between prepregnancy body mass index (BMI) and childhood asthma development (aim 1), evaluate potential mediating pathways between prepregnancy BMI and childhood asthma risk (aim 2), and explore the role of GWG on risk of childhood asthma (aim 3). We investigated these questions using electronic medical records from a large cohort of over 100,000 mother-child pairs enrolled in Kaiser Permanente Northern California (KPNC) who gave birth between 2005-2014.

First, we estimated the risk of childhood asthma for increasing prepregnancy BMI among those followed up to ages 4, 6, and 8 years, defining asthma using a combination of diagnostic codes and controller medication dispensings, and including prepregnancy BMI obese subclasses. Second, we assessed potential intermediate factors between prepregnancy BMI and childhood asthma, namely GWG (delivery weight minus prepregnancy weight), gestational age, and the child's own BMI. Third, we evaluated the association between GWG and childhood asthma while operationalizing GWG several different ways including total GWG (continuous and categories), observed GWG compared to Institutes of Medicine (IOM) recommended ranges of GWG, and trimester-

specific GWG (total and rates); we also implemented the parametric g-formula to account for the time-varying nature of GWG and to control for time-varying confounding.

In our first study, we found that higher prepregnancy BMI was modestly associated with increased childhood asthma risk, even after controlling for important confounding variables. Our second study showed that childhood obesity did have a modest mediating effect on the association between prepregnancy BMI and childhood asthma, but there was no evidence for gestational age or GWG as intermediate factors. In our third study, we observed a null association between GWG metrics and childhood asthma development, even when controlling for time-varying confounding.

Collectively, these findings suggest evidence for a causal link between prepregnancy obesity and childhood asthma development, potentially partially mediated through the child's own obesity. These findings did not show evidence for an effect of GWG on childhood asthma. Even though the studies presented in this dissertation are valuable additions to the existing literature, further investigation of potential mechanisms and preventative interventions is needed. Understanding of biological mechanisms and interventions would not only benefit pregnant women but would also have positive impacts on reducing childhood asthma risk.

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Chapter 1: Introduction

Background

Childhood Asthma

The most common chronic condition among children is asthma.[1] In 2019, the United States (US) Centers for Disease Control and Prevention (CDC) reported that over 5.1 million children under the age of 18 had asthma.[2] Additionally, asthma is the third leading cause of hospitalizations among children,[3] though deaths due to asthma are rare.[1] Nearly 50% of children experience at least one episode of wheezing before the age of 6,[4] and one-third of children have a wheezing episode before age 3.[5] Though only 25% of these children go on to develop asthma since sometimes those symptoms go away as they grow, and their lungs develop.[4,5]

Asthma makes it difficult for air to move in and out of the lungs due to inflammation, which can cause wheezing, chest tightness, breathlessness, and coughing.[1] Due to the increased sensitivity of the lungs, certain triggers or exposures can cause asthma episodes (or 'attacks').[6] These episodes can cause the airway linings to swell, airway mucus secretion to increase, and muscles surrounding the airways to tighten.[6] Some common triggers can include second-hand smoke, respiratory infections and allergens.[7]

Diagnosing asthma includes a physician evaluating symptoms, investigating health history, and a physical exam.[8] Physicians will ask about the frequency and severity of symptoms. They will also ask about the child's medical history including any family members that have asthma, allergies, and exposure to second-hand smoke or pollutants.

In addition, physicians will have children perform breathing tests (typically to test lung function). Since asthma can be difficult to diagnose in young children (aged $\leq$ 5 years), asthma-like symptoms among young children are commonly classified as 'preschool wheezing'.[5]

There are several effective treatments for childhood asthma including medications and lifestyle changes.[9] Medications include quick-relief and/or long-term bronchodilators, inhaled corticosteroids, and sometimes antibiotics.[9] Physicians may even recommend lifestyle changes such as reduced second-hand smoke exposure, weight loss, or avoiding asthma triggers.

Many studies have investigated risk factors for childhood asthma. Some of the most prominent risk factors include genetic factors, preterm birth, exposure to allergens, smoke, air pollution, diet/nutrition, and obesity.[10] In recent years, prenatal exposures that could potentially increase the risk of childhood asthma have been examined. Prenatal exposures (i.e., maternal smoking, stress, obesity, and infections) could influence fetal growth, the development of the lungs and airways, and the immune system function through either direct or indirect mechanisms.[10]

Prepregnancy Body Mass Index (BMI)

Obesity (BMI $\geq$30 kg/m^2) is known to be worldwide epidemic.[11] In the US we have seen a significantly increasing trend in the prevalence of prepregnancy obesity from 2016 to 2019. Overall prepregnancy obesity increased 11% from 26.1% in 2016 to 29.0% in 2019.[12] Increases in prepregnancy obesity were seen for women of all age groups, all race and ethnicity groups, and all education levels.[12] Prepregnancy obesity also increased in all US states (except for Vermont) with increases from 4% (District of Columbia [DC])

to 22% (Mississippi).[12] Prepregnancy obesity has been found to be associated with increased risk of pregnancy complications such as preeclampsia, gestational diabetes, and complicated deliveries.[13]

Gestational Weight Gain (GWG)

GWG describes the weight gained during pregnancy. In 2009, the Institute of Medicine (IOM) updated the recommendations for ideal ranges of weight gain during pregnancy tailored by prepregnancy BMI group.[14] Previously these recommendations were developed to minimize the risk of low birthweight and preterm births.[15] Though, the 2009 update also considered maternal and infant outcomes associated with gestational weight gain which included small-or-large-for gestational age, unplanned cesarean delivery, and excessive postpartum weight retention (≥11 lbs.).[15] The recommended weight gain in the first trimester is the same for all women (1.1-4.4 lbs.), but in the second and third trimester guidelines differ by BMI categories.[14] For example, those starting with lower prepregnancy BMIs have higher weight gain recommendations. Several studies have also highlighted the relationship between prepregnancy BMI and GWG. In general women with overweight and obese prepregnancy BMIs will gain less weight (on average) than women with underweight and normal prepregnancy BMIs.[16,17] However, women with overweight or obese prepregnancy BMIs are more likely to exceed GWG recommendations compared to women with underweight and normal prepregnancy BMIs.

Biological Mechanisms

There are no clear biological mechanisms linking prepregnancy BMI, GWG, and childhood asthma. Though, if prepregnancy BMI and GWG do truly affect child's asthma

risk one plausible mechanism is through inflammatory pathways. Pregnancy itself gives rise to proinflammatory conditions, especially in the first trimester an important time for immune development, and is considered a natural inflammatory state, characterized by increases in serum pro-inflammatory cytokine levels.[18,19]

Prepregnancy obesity is associated with chronic inflammation as adipose tissue secretes inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α).[19] This chronic inflammation can alter a woman's microbiome and subsequently during pregnancy the microbiome of the fetus.[20] Alterations in the microbiome of the lungs and/or intestines can shape early immunological development, thus contributing to immune deficiencies associated with asthma development in childhood.[20,21] 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.[20,22]

Excessive weight gain can also cause increases in inflammation during pregnancy, though since rates of weight gain differ by trimester, this may be most impactful during the first trimester. [23,24] Inflammatory markers (such as IL-6, high sensitivity C-reactive protein, and serum amyloid A) can increase 18%-25% in women with high amounts of weight gain during pregnancy.[23] Changes in the fetal microbiome due to increases in circulating inflammatory markers caused by excessive amounts of GWG can influence early immunological development and cause immune deficiencies associated with asthma development in childhood.[21]

Current Literature

There is a growing body of evidence to suggest that there is a positive association between maternal prepregnancy obesity and development of wheeze or asthma in childhood. In the past decade, many studies have reported a positive association between maternal obesity and childhood asthma and/or wheeze. These studies were predominately observational cohort studies that collected maternal height and weight measurements before pregnancy or in early pregnancy and assessed childhood wheezing and asthma at different ages (e.g., 0-5 years or 6-8 years).

One of the largest studies, including 38,874 children, found positive associations between maternal BMI overweight and obese categories compared to normal BMI and childhood asthma ever (BMI 25-30: odds ratio [OR]=1.22, 95% confidence interval [CI]=1.12, 1.33; BMI 30-35: OR=1.56, 95% CI=1.36, 1.79; BMI >35: OR=1.55, 95% CI=1.23, 1.95).[25] Another large study, including over 30,000 children, found that maternal obesity (BMI>30) was positively associated with wheezing in 18-month old children (risk difference [RD] = 3.3; 95% CI: 1.2-5.3), though no association was found for maternal overweight (BMI 25-30).[26] Additionally, in a pooled analysis of 85,509 children from 14 different European birth cohorts, the authors found that both maternal overweight (BMI 25-30) and obesity (BMI>30) were positively associated with any wheezing (BMI 25-30 OR=1.08, 95% CI=1.05, 1.11; BMI >30 OR=1.12, 95% CI=1.08, 1.17) and recurrent wheezing during the first two years of life (BMI 25-30 OR=1.19, 95% CI=1.12-1.26; BMI >30 OR=1.16, 95% CI=0.97-1.39).[27]

Though most studies use maternal prepregnancy BMI categories for analyses, a few other studies use continuous prepregnancy BMI and continue to find a positive

association between prepregnancy BMI and childhood asthma and wheeze. One study

found that a one unit (kg/m^2) increase in prepregnancy BMI was associated with

increased odds of reporting transient early wheeze (OR=1.16, 95% CI=1.03, 1.30) and

persistent wheeze (OR=1.26, 95% CI=1.01, 1.57) in children aged 8 years old.[28] Another

study using continuous prepregnancy BMI found positive associations between a one unit

increase in prepregnancy BMI and asthma ever (OR=1.06, 95% CI=0.91, 1.24), current

asthma (OR=1.10, 95% CI=0.92, 1.32), wheeze ever (OR=1.08, 95% CI=1.02, 1.13), and

current wheeze (OR=1.02, 95% CI=0.87, 1.20) in children aged 6 years old, though some

associations were not significant.[29]

Fewer studies have investigated the role of GWG in a child's risk of developing

asthma or wheeze and results have been inconsistent. One large study found that children

whose mothers gained more than 20 kg during their pregnancy, compared to mothers who

gained 10-15 kg, had higher odds of asthma ever (20-24 kg OR=1.15, 95% CI=1.05-1.27;

>25kg OR=1.19, 95% CI=1.04, 1.35) and current asthma (20-24 kg OR=1.15, 95%

CI=1.01-1.31; >25kg OR=1.23, 95% CI=1.03, 1.46) at age 7.[25] Another study found an

overall increase in odds of wheeze from 1-4 years old per standard deviation (4.7 kg)

increase in GWG (OR=1.09, 95% CI=1.04, 1.14).[30] This study also found that when

stratified by prepregnancy BMI, the strongest effect of GWG on overall wheezing in the

child from aged 1-4 years was among normal BMI (20-24.9 BMI OR=1.08, 95%

CI=1.01-1.15) and overweight mothers (25-29.9 BMI OR=1.18, 95% CI=1.06-1.31) per

standard deviation increase in GWG.[30] A pooled analysis of 4 studies analyzed

continuous GWG and found that there was a positive association for each 1 kg increase in

GWG for current asthma or wheeze (OR=1.01, 95% CI=1.01, 1.02) and asthma or

wheeze ever (OR=1.04, 95% CI=0.97, 1.11), though it was not significant.[31] This pooled

analysis also found that children born to mothers in the highest GWG groups (>15 kg)

had increased odds of asthma or wheeze ever (OR=1.16, 95% CI=1.00, 1.34), but not

current asthma or wheeze (OR=1.08, 95% CI=0.89, 1.30).[31]

Table 1.1 Review of articles on prepregnancy obesity, gestational weight gain, and childhood asthma/wheeze

Citation, Location, Time Period	Study Type, Sample Size	Exposure	Outcome	Covariates	Results
Oliveti et al., 1996[32] United States (OH) 1990	Case-Control N=262	GWG, medical records	Childhood asthma at ages 4-9, medical records	Maternal asthma history, smoking, prenatal care, bronchiolitis, use of oxygen at birth, preterm birth, birth weight, and 5-min Apgar score	Asthma: GWG <9 kg OR:3.42 (95%CI: 1.72, 6.79)
Rusconi et al., 2007[33] Italy 1994-1995	Cohort N=15,609	GWG, self-reported	Childhood wheeze at age 6-7, self-reported	Maternal age, education, smoking, parental asthma or atopy, socioeconomic status, siblings, birth weight, child's sex, season, and study center	Persistent wheezing (compared to GWG 9-15 kg): GWG <9 kg OR:1.08 (95%CI: 0.84, 1.39) GWG >15 kg OR:1.20 (95%CI: 0.98,1.48)
Reichman and Nepomnyaschy 2008[34] United States 1998-2000	Cohort N=1,971	Maternal prepregnancy BMI, medical records	Childhood asthma at age 3, self-reported	Maternal age, education, race, income, smoking, preterm delivery, child's sex, child's age, child's BMI	Asthma ever: BMI>30 OR:1.34 (95%CI: 1.03, 1.76)
Håberg et al., 2009[35] Norway 1999-2005	Cohort N=32,281	Maternal prepregnancy BMI, self-reported	Childhood wheeze at 18 months, self-reported	Maternal age, education, income, asthma, smoking, parity, cesarean section, birth weight, preterm birth, child's sex, breastfeeding and day care	Wheeze: BMI 25-30 RD: 0.4 (95%CI: 1.1,1.8) BMI >30 RD: 3.3 (95%CI: 1.2,5.3)
Kumar et al., 2010[36] United States (MA) 1998	Cohort N=1,191	Maternal prepregnancy BMI, self-reported	Childhood recurrent wheeze at age 3, self-reported	Maternal age, race, education, atopy, smoking, premature delivery, fetal growth retardation, large size for gestational age and child's sex	Wheezing (compared to BMI <25): BMI 25-30 OR: 1.58 (95%CI: 0.75, 3.30) BMI >30 OR:3.51 (95%CI: 1.68,7.32)
Scholtens et al., 2010[37] Netherlands 1996-1997	Cohort N=3,963	Maternal prepregnancy BMI, self-reported	Childhood wheeze and asthma up to age 8, self-reported	Maternal education, smoking, asthma, mode of delivery, birth weight, breastfeeding and child's BMI	Family history asthma/atopy (continuous BMI): Asthma OR:1.05 (95%CI: 1.01, 1.10) Wheeze OR:1.06 (95%CI: 1.01, 1.12) No family history asthma/atopy (continuous BMI): Asthma OR:0.98 (95%CI:0.94, 1.02) Wheeze OR:1.01 (95%CI: 0.69, 1.07)
Lowe et al., 2011[38] Sweden 1998-2009	Cohort N=189,783	Maternal prepregnancy	Childhood asthma up to age 10,	Maternal age, parity, birth year, singleton, country, smoking, maternal asthma, maternal	Asthma (compared to BMI 18.5-24.9) BMI <18.5 RR:0.97 (95%CI: 0.75, 1.25) BMI 25-29.9 RR:1.18 (95%CI: 1.06, 1.31)

		BMI, medical records	hospital admission and prescriptions	diabetes and hypertension, pregnancy complications, child's sex, gestational age, birth weight, and cesarean section,	BMI 30-34.9 RR:1.40 (95%CI:1.16, 1.68) BMI >35 RR:1.01 (95%CI:0.90, 1.14)
Patel et al., 2012[39] Northern Finland 1985-1986	Cohort N=6,945	Maternal prepregnancy BMI, medical records	Childhood wheeze and asthma at age 15-16, self-reported	Maternal education, maternal asthma, socioeconomic status, marital status, parental smoking, birth weight, and child BMI	Continuous BMI (per 1kg/m^2 increase) Ever wheeze or asthma OR:1.03 (95%CI: 1.01, 1.05) Current wheeze or asthma OR:1.05 (95%CI: 1.02, 1.08)
Caudri et al., 2013[28] Netherlands 1996-1997	Cohort N=3,963	Maternal prepregnancy BMI, self-reported	Childhood wheeze at age 8, self-reported	Maternal age, parental education, maternal asthma, parental allergies, smoke exposure, siblings, pregnancy duration, birth weight, child sex, breastfeeding, day care, and study region	Persistent wheeze (compared to never/infrequent wheeze): Continuous BMI OR:1.06 (95%CI: 0.99,1.50)
Guerra et al., 2013[40] Spain 2004-2008	Cohort N=1,107	Maternal prepregnancy BMI, self-reported	Childhood wheeze at 14 months, self-reported	Maternal age, socioeconomic status, parental asthma, smoking, parity, type of delivery, preterm birth, birth weight, child sex, day care, and breastfeeding	Frequent wheeze (compared to BMI 18.5-25): BMI <18.5 OR:1.7 (95%CI: 0.3,8.3) BMI 25-30 OR:1.0 (95% CI: 0.4,2.6) BMI>30 OR:4.2 (95% CI: 1.5,11.3) Continuous BMI OR: 1.08 (95%CI: 1.01,1.15)
Halonen et al., 2013[41] United States (AZ) 1996-2004	Cohort N=261	Maternal prepregnancy BMI, medical records; GWG, objective measured	Childhood asthma up to age 9, physician diagnosed (active symptoms, or prescription medications)	Maternal age, ethnicity, parental smoking, parity, and child's sex.	Childhood Asthma (compared to low tertile[s]): BMI (mid tertile) OR:0.5 (95%CI: 0.2, 1.3) BMI (high tertile) OR:0.4 (95%CI: 0.2, 1.1) GWG (high tertile) OR:3.4 (95%CI: 1.6, 7.2)
Harpsøe et al., 2013[25] Denmark 1996-2002	Cohort N=38,874	Maternal prepregnancy BMI, self-reported; GWG, self-reported	Childhood asthma at age 7, physician diagnosed (self-reported)	Maternal age, race, socioeconomic status, smoking, atopy, cesarean delivery, parity, child sex, and day care use	Asthma ever:(compared to BMI 18.5-25): BMI <18.5 OR:1.03 (95%CI: 0.88, 1.22) BMI 25-30 OR:1.22 (95%CI: 1.12, 1.33) BMI 30-35 OR:1.56 (95%CI: 1.36, 1.79) BMI >35 OR:1.55 (95%CI: 1.23, 1.95) GWG (compared to 10-15 kg): GWG <5 kg OR:1.17 (95%CI: 0.94, 1.45) GWG 5-9 kg OR:1.02 (95%CI: 0.91, 1.15) GWG 16-19 kg OR:0.97 (95%CI: 0.89, 1.06)

					GWG 20-24 kg OR:1.15 (95%CI: 1.05, 1.27) GWG >25 kg OR:1.19 (95%CI: 1.04, 1.35)
Leermakers et al., 2013[30] Netherlands 2002-2006	Cohort N=4,656	Maternal prepregnancy BMI, self-reported GWG, self-reported/ measured	Childhood wheeze up to age 4, self-reported	Maternal age, ethnicity, education, smoking, gestational complications, parity, gestational age, birth weight, child's sex, breastfeeding day care, pets, and child's height and weight at follow-up	Wheezing (continuous BMI) With maternal history of asthma/atopy OR:1.02 (95%CI: 0.96, 1.08) Without maternal history of asthma/atopy OR:1.07 (95%CI: 1.00, 1.15) Wheezing (per SD [4.7 kg] increase): GWG OR (BMI <20):1.06 (95%CI:0.90, 1.23) GWG OR (BMI 20-25):1.08 (95%CI:1.01, 1.15) GWG OR (BMI 25-30):1.18 (95%CI:1.06, 1.31) GWG OR (BMI>30):1.03 (95%CI:0.90, 1.17)
Pike et al., 2013[29] United Kingdom 1998-2002	Cohort N=940	Maternal prepregnancy BMI, objective measure	Childhood wheeze and asthma up to age 6, self-report/ physician diagnosis	Maternal education, asthma, smoking, parity, birth weight, child's sex and breastfeeding	Continuous BMI (per 1kg/m^2 increase) Asthma ever OR:1.06 (95%CI: 0.91, 1.24) Current asthma OR:1.10 (95%CI: 0.92,1.32) Wheeze ever OR:1.08 (95%CI: 1.02, 1.13) Current wheeze OR:1.02 (95%CI: 0.87,1.20)
Wright et al., 2013[42] United States (MA) 2002-2007	Cohort N=261	Maternal prepregnancy BMI, self-reported	Childhood wheeze up to age 2, self-reported	Maternal age, education, race, prenatal smoking, atopy, serum cortisol levels, birth weight, gestational age, child's sex	Repeated Wheeze: BMI>30 OR:2.65 (95%CI: 1.01, 6.95)
de Vries et al., 2014[43] Netherlands 2003-2004	Cohort N=4,860	Maternal prepregnancy BMI, self-reported	Childhood wheeze at 3-5 months, self-reported	Maternal education, smoking, child's sex, breastfeeding, season	Wheeze: Continuous BMI (1kg/m^2) OR:1.03 (95%CI: 1.00, 1.05)
Ekström et al., 2015[44] Sweden 1994-1996	Cohort N=3,294	Maternal prepregnancy BMI, medical records	Childhood asthma up to age 16, self-reported	Maternal age, parental allergies, socioeconomic status, smoking, siblings, child's sex	Asthma: Continuous BMI (5kg/m^2) OR:1.23 (95%CI: 1.07, 1.40)
Harskamp-van Ginkel et al., 2015[45] Netherlands 2003-2004	Cohort N=3,185	Maternal prepregnancy BMI, self-reported	Childhood wheeze and asthma at ages 7-8, self-reported	Maternal age, maternal education, ethnicity, parental asthma, smoking, parity, gestational age, caesarean section, child's sex, birth weight, breastfeeding and child's BMI	Prepregnancy BMI (continuous) Asthma RR:2.32 (95%CI:1.49, 3.61) Wheeze RR:2.16 (95%CI: 1.28, 3.64)
Dumas et al., 2016[46] United States 1996-1999	Cohort N=12,963	Maternal prepregnancy BMI, self-reported	Childhood asthma at ages 9-14, self-reported/ physician diagnosed	Maternal age, race, ethnicity, maternal asthma, smoking, income, parental education, region, mode of delivery, birth	Prepregnancy BMI (compared to BMI 20-22.5): BMI <20 OR:1.05 (95%CI: 0.94, 1.18) BMI 22.5-25 OR:1.01 (95%CI: 0.89, 1.14) BMI 25-30 OR:1.19 (95%CI: 1.03, 1.38)

				weight, breastfeeding, and birth order	BMI >30: OR:1.34 (95%CI: 1.08, 1.68) GWG (compared to GWG 25-34 lbs): GWG <15 OR:1.28 (95%CI: 0.98, 1.66) GWG 15-24 OR:1.07 (95%CI: 0.95, 1.20) GWG 35-44 OR:1.04 (95%CI: 0.93, 1.17) GWG >45: OR:1.05 (95%CI: 0.92, 1.21)
Taylor-Robinson et al., 2016[47] United Kingdom 2000-2002	Cohort N=11,141	Maternal prepregnancy BMI, self-reported	Childhood wheeze up to age 7, self-reported	Maternal age, ethnicity, maternal asthma/atopy, smoking, cesarean section, preterm birth, child sex, siblings, breastfeeding, pollution exposure, pets, and child care	Persistent wheeze (vs never): BMI <18.5 RR:1.10 (95%CI: 0.79, 1.52) BMI 18.5-24.9 RR:1.00 (95%CI:1.00, 1.00) BMI 25-29.9 RR:1.25 (95%CI: 1.05, 1.48) BMI 30-39.9 RR:1.38 (95%CI: 1.06, 1.80) BMI >40 RR:1.57 (95%CI: 1.01, 2.45)
Polinski et al., 2017[48] United States 2001	Cohort N=6,450	Maternal prepregnancy BMI, self-reported GWG, birth certificate/ self-reported	Childhood asthma up to age 4, self-reported/ physician diagnosis	Maternal age, race, smoking, parity, gestational age, birth weight, child's sex, participation in assistance programs	Prepregnancy BMI (compared BMI 18.5-25) BMI <18.5 OR:1.04 (95%CI: 0.70, 1.54) BMI 25-29.9 OR:1.25 (95%CI: 0.99, 1.59) BMI >30 OR:1.63 (95%CI: 1.26, 2.12) GWG Continuous (kg) OR:1.00 (0.98, 1.02) Trimester rate (kg/week) OR:1.08 (0.69, 1.71) IOM (compared to adequate) Inadequate OR:0.99 (95%CI: 0.76, 1.32) Excessive OR:0.85 (95%CI: 0.68, 1.08) Categories (compared to 10-15 kg) <5 kg OR:1.56 (95%CI: 1.04, 2.35) 5-9 kg OR:1.06 (95%CI: 0.82, 1.37) 16-19 kg OR:0.84 (95%CI: 0.62, 1.13) 20-24 kg OR:1.16 (95%CI: 0.85, 1.59) >25 kg OR:1.53 (95%CI: 0.99, 2.35)
Rajappan et al., 2017[49] United Kingdom 1998-2002	Cohort N=2,799	Maternal prepregnancy BMI, objective measure	Childhood wheeze at 6 and 12 months, self-reported	Maternal age, height, education, parity, late pregnancy 25-hydroxyvitamin D status, smoking, asthma, paternal age, height, asthma, BMI, birth weight, gestational age, breastfeeding and	Wheeze (per 5kg/m^2): BMI RR:1.09 (95%CI: 1.05, 1.13) Wheeze (compared to BMI 18.5-24.9): BMI <18.5 RR:0.70 (95%CI: 0.44, 1.11) BMI 25-29.9 RR:1.08 (95%CI: 0.98, 1.20) BMI >30 RR:1.19 (95%CI:1.06, 1.34)

		GWG, objective measure		adiposity gain between birth and 6 months	Wheeze (compared to adequate GWG) Inadequate RR:1.05 (95%CI: 0.92, 1.19) Excessive RR:0.97 (95%CI: 0.87, 1.09)
Goudarzi et al., 2018[50] Japan 2003-2012	Cohort N=3,296	Maternal prepregnancy BMI, self-reported	Childhood wheeze up to age 7, self-reported	Maternal age, education, allergies, smoking, child's sex, birth weight, child's BMI, child's comorbid allergic diseases	Wheeze (per kg/m^2) BMI RR:1.03 (95%CI: 1.00, 1.06)
Chen et al., 2020[51] China 2019	Cross-Sectional N=8,877	Maternal prepregnancy BMI, self-reported GWG, self-reported	Childhood asthma up to age 14, self-reported	Maternal age, paternal age, income, parity, maternal and paternal smoking, alcohol use, and family history of atopy	Asthma (compared to BMI 18.5-22.9) BMI <18.5 PR:0.95 (95%CI: 0.97, 1.03) BMI >23 PR:1.04 (95%CI:0.96, 1.13) Asthma (compared to GWG 10-15 kg) GWG <10 kg PR:0.90 (95%CI: 0.82, 0.98) GWG 15-25 kg PR:1.13 (95%CI: 1.06, 1.21) GWG >25 PR: 1.22 (95%CI: 1.08, 1.38) Asthma (compared to adequate GWG) Inadequate PR:0.87 (95%CI: 0.80, 0.93) Excessive PR:1.12 (95%CI: 1.04, 1.20)
Polinski et al., 2020[52] United State (NY) 2008-2019	Cohort N=5,939	Maternal prepregnancy BMI, birth certificate GWG, self-reported	Childhood wheeze up to age 3 and asthma at age 7-9, self-reported/ physician diagnosed	Maternal age, race, ethnicity, education, health insurance, maternal atopy, marital status, smoking, gestational diabetes, birth weight, and gestational age	Wheeze (compared to BMI 18.5-24.9): BMI <18.5 RR:0.93 (95%CI: 0.42, 2.09) BMI 25-29.9 RR:1.24 (95%CI: 0.93, 1.65) BMI 30-34.9 RR:1.45 (95%CI:1.03, 2.03) BMI >35 RR:1.51 (95%CI:1.08, 2.11) Wheeze (compared to adequate GWG) Inadequate RR:1.00 (95%CI: 0.72, 1.38) Excessive RR:0.93 (95%CI: 0.71, 1.21) Asthma (compared to BMI 18.5-24.9): BMI <18.5 RR:1.62 (95%CI: 0.85, 3.06) BMI 25-29.9 RR:1.28 (95%CI: 0.92, 1.78) BMI 30-34.9 RR:1.05 (95%CI:0.67, 1.64) BMI >35 RR:1.12 (95%CI:0.74, 1.70) Asthma (compared to adequate GWG) Inadequate RR:1.26 (95%CI: 0.84, 1.91) Excessive RR:1.00 (95%CI: 0.72, 1.39)

Srugo et al., 2021[53] Canada 2012-2014	Cohort N=248,017	Maternal prepregnancy BMI, objective measure GWG, objective measure	Childhood asthma at age 7, medical records	Maternal age, maternal pre-existing conditions, smoking, alcohol/illicit drug use, medications use, rurality, socioeconomic status, parity, and child's sex	Asthma (compared to BMI 18.5-24.9) BMI <18.5 HR:0.97 (95%CI: 0.92, 1.02) BMI 25-29.9 HR:1.03 (95%CI: 1.00, 1.06) BMI >30 HR:1.08 (95%CI: 1.05, 1.11) Asthma (compared to adequate GWG) Inadequate HR:1.01 (95%CI: 0.97, 1.04) Excessive HR:1.03 (95%CI: 1.00, 1.06)

Abbreviations: GWG – gestational weight gain, OR – odds ratio, CI – confidence interval, BMI – body mass index, RD – risk difference, RR – risk ratio, HR – hazard ratio, PR – prevalence ratio

Gaps and Limitations

Prepregnancy BMI

Previous studies are inconsistent in the definition and collection of prepregnancy BMI. Studies calculate prepregnancy BMI from height and weight measurements using a standard formula (weight in kg divided by height in meters squared).[11] Though, height and weight measurement timing can vary from before pregnancy, during pregnancy, to even after pregnancy when women are asked to recall this information. While most studies use the standard definitions for BMI categories from 2000[11] (underweight BMI <18.5, normal BMI =18.5-25, overweight BMI =25-30, and obese BMI >30), some studies include the very obese (BMI >35) category and others do not. Currently, few studies include the distinction of the newly defined obese class 1, 2, and 3 categories (obese class 1 BMI =30-35, obese class 2 BMI =35-40, and obese class 3 BMI >40). It is important to consider that women previously grouped in the outdated obese category (BMI>30) have different relationships to other important variables in the study depending on their finer level of BMI (i.e., further stratification is required).

Furthermore, studies have been inconsistent with how they handle prepregnancy BMI in their analyses. Some studies chose to use the defined BMI categories, using normal BMI as the reference. Though these studies often leave out the underweight BMI category (usually due to small sample size). Or these studies use prepregnancy BMI as a continuous variable and express their results in 1 or 5 unit increases (kg/m^2) or by less interpretable standard deviation increases.

GWG

In the current literature, the definition and collection of GWG is also inconsistent. The characterization of GWG depends heavily on the methods used to collect maternal weight data. For the purposes of this discussion, two methods are single weight measurements or serial weight measurements. The single weight measurement method characterizes GWG as the total weight gained throughout the pregnancy, often calculated as the last weight measurement (commonly the weight measured at the time of delivery) minus prepregnancy weight.[54] Serial weight measurements over the course of pregnancy can be used to characterize the longitudinal pattern of weight gain, often by using several weight measurements to model the trajectory of the weight gained during pregnancy. Longitudinal studies or retrospective studies of medical records that collect multiple weight measurements often define GWG both ways, but the application of repeated weight measurements can be difficult to execute properly as the timing and number of measurements can vary widely. Using total GWG instead of repeated measures limits the interpretation of results to the effect of the total weight gained throughout pregnancy and not the effect of the pattern of weight gain or effect of trimester-specific GWG. Additionally, many studies will exclude mothers who lost weight during their pregnancy (i.e., total GWG <0).

Furthermore, studies have been inconsistent with how they handle GWG in their analyses. Using total GWG during pregnancy, some studies will analyze this as a continuous variable, using either one-, five-, or 10-unit (kg, lbs.) increases or categories (5-10 kg increments or 10 lbs. increments). Other studies will compare the total GWG to the IOM guidelines (inadequate, adequate, or excessive).[14] Studies using repeated weight gain measurements seem to take different analytic approaches with varying degrees of

complexity, often giving results that are difficult to interpret or incomparable to other studies. For newer results to be comparable to previous studies, several analytical approaches must be utilized.

The single weight measurement method (total GWG) is often used due to limited data collection or data availability. Prepregnancy weight and delivery weight are reported on birth certificates (as of the 2003 revision)[55] and are often abstracted into population-level databases. Though this allows these data to be easily obtained for large observational studies, there are some limitations. While entries of prepregnancy weight and delivery weight are often non-missing (<10%) they have been shown to not always be accurate with poor reporting of prepregnancy weight among those who had very low or very high weight gain.[55] Self-reported prepregnancy weight and delivery weight can also be used in the single weight measurement method and is often more accurate.[56]

A common application of this method in analyses is to compare the total weight gained during pregnancy to the IOM guidelines for ranges of weight gain for term pregnancies.[14] This is done by categorizing the women's total weight gain as below, within, or above these guidelines, which are specific for each prepregnancy BMI category. However, this method ignores the fact that women who are pregnant longer have more opportunity to gain weight.[14,54] This method also does not describe the pattern of weight gain throughout pregnancy which can be important for outcomes that are sensitive to high or low weight gain during certain periods of pregnancy.[57]

The method of using single weight measurements does not account for the pattern of weight gained during pregnancy. Using serial weight measurement methods instead can describe the trajectory of weight gained during pregnancy. Describing the trajectory

of weight gain or at least considering that the longitudinal pattern of weight gain is not

linear throughout a pregnancy can be important for specific outcomes that are sensitive to

high or low weight gain during certain periods of pregnancy (i.e., childhood obesity).[58,59]

Serial weight measurements are often obtained directly by researchers in cohort studies

(physical measurements or self-reported) or by obtaining medical records of prenatal

visits and delivery records.

It is clear that discussions on the effects of GWG on child outcomes, like

childhood asthma, must include maternal prepregnancy BMI.[14] Current guidelines for

recommended amounts of weight gain during pregnancy are categorized by prepregnancy

BMI. It is important that results from studies evaluating GWG as an exposure consider

this in the design, analysis, and presentation of results. Prepregnancy BMI can be used as

an additional exposure variable but should also be assessed as a potential effect modifier

of the relationship between GWG and the outcome of interest. Doing so can identify if

some groups are at higher risk of an adverse outcome or receive more benefit from an

intervention. This can be particularly important when discussing new recommendations,

strategies, or policies.[54]

One common way to assess effect modification of prepregnancy BMI on the

association between GWG and the outcome of interest is to conduct a stratified analysis.

This method is simple and commonly stratifies based on pre-defined BMI categories,[11]

though doing so will not describe the effect of prepregnancy BMI on the outcome of

interest. Another method is to use multivariate regression models with a cross-product

term between prepregnancy BMI and GWG. In this approach, BMI can be defined as

continuous or using categories which can reduce the potential for residual confounding

and incomplete estimation of effect modification. Using multivariate regression models also has the advantage of being more statistically efficient to stratified models[60] and may be preferred when sample sizes are limited.

Gestational Duration

It is important to consider the relationship between GWG and gestational duration. Both vary over time but are often treated as fixed variables such as total GWG and gestational age at delivery (commonly due to data availability). Total GWG (delivery weight – prepregnancy weight) is a summary measure expressing the accumulation of weight gained (or lost) throughout pregnancy. Similarly, gestational age at delivery is a summary of indicator variables indicating whether or not a baby was born at a given week of gestation. Birthweight can also be added to the mix, given that it is a summery measure of the accumulation of fetal weight throughout gestation, and is associated with both gestational weight and gestational duration. At any given week of gestation, the current gestational weight, gestational age, and/or fetal weight can affect each other variable and influence their trajectory throughout pregnancy. To help visualize these relationships throughout gestation, Hinkle et al.,[61] included a directed acyclic graph (DAG) in their paper discussing this topic (Figure 1.1).

The DAG (Figure 1.1)[61] shows that whether or not a woman remains pregnant (IU) at a given week can impact subsequent gestational (MW) and fetal weight (FW) gain. Additionally, the longer a woman remains pregnant the more opportunity she has to continue to gain weight. GWG can impact future fetal weight gain as well as the probability of delivery at any given gestational week. Similarly, fetal weight gain can impact future gestational weight gain as well as the probability of delivery at a given

gestational week. The DAG also shows that total GWG, gestational age at delivery and birthweight are summary measures of the longitudinal advancement of gestational weight, the length of pregnancy and fetal weight throughout pregnancy.

Figure 1.1 DAG from Hinkle et al., (2016)[61] showing relationship between gestational weight gain and gestational duration
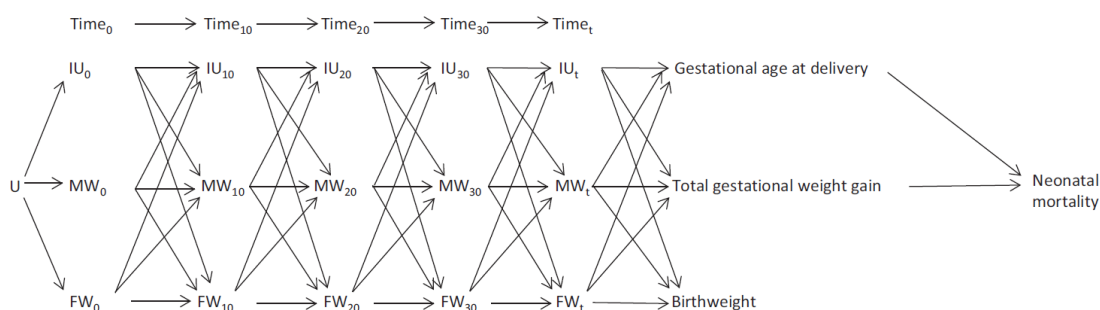
Figure 1. Directed acyclic graph representing the longitudinal relations between maternal weight gain, foetal weight, and gestational age. Where IU represents if the baby is still *in utero*, MW represents maternal weight gain including maternal, foetal and placental tissue and fluid expansion, and FW represents foetal weight.

This relationship is of particular importance when the outcome of interest is also associated with gestational age (e.g., neonatal mortality as noted in Figure 1.1).[61] Commonly, this is a major issue for studies that use the summary measures of GWG and gestational age. Failure to properly acknowledge and properly account for gestational age in these studies can result in estimated associations that are biased.[57]

The type of bias can be determined by the theoretical DAG used to frame the relationships between variables. Figure 1.2 and Figure 1.3 are two example DAGs also included by Hinkle et al.,.[61] Both DAGs can be used to represent the association between total GWG and an outcome that is also associated with gestational age (in this case neonatal mortality). U represents the longitudinal process described above in Figure 1.1,[61]

and C represents measured or unmeasured confounders of the association between gestational age at delivery and neonatal mortality (or outcome associated with gestational age).

In Figure 1.2,[61] it is clear there is a backdoor path from total gestational weight gain to neonatal mortality (through U and gestational age at delivery). This can easily be blocked by controlling for gestational age at delivery analytically (such as including it as a covariate in a regression model). Upon controlling for gestational age at delivery, the backdoor path is blocked removing the confounding bias caused by gestational age at delivery on the association between total gestational weight gain and neonatal mortality.

Figure 1.2 DAG from Hinkle et al., (2016)[61] highlighting confounding bias
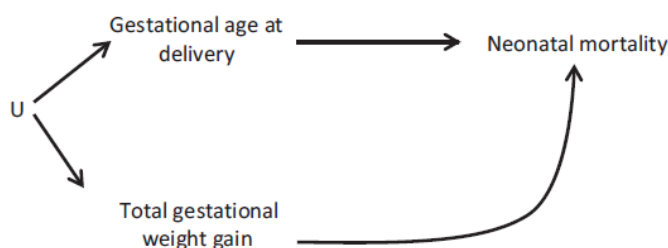
In Figure 1.3,[61] while the same backdoor path between total GWG and neonatal mortality exists, adjusting for gestational age at delivery now induces collider bias,[62] due to the confounder present between gestational age at delivery and neonatal mortality. If the confounder between gestational age at delivery and neonatal mortality is measured, the solution is simple: control for that confounder instead of gestational age at delivery. This will still remove the confounding bias without inducing collider bias. However, if

the confounder(s) are unmeasured, there is no way to completely eliminate either bias.

The magnitude of the bias, in this situation, depends on the strength of the relationship

between the unmeasured confounder C, gestational age at delivery and neonatal mortality

(or other outcome associated with gestational age).[61] Typically, collider bias is smaller in

magnitude than confounding bias, though this has yet to be validated in the causal

structures dealing with GWG, gestational age and maternal or infant outcomes.[63,64]

Figure 1.3 DAG from Hinkle et al., (2016)[61] highlighting collider bias
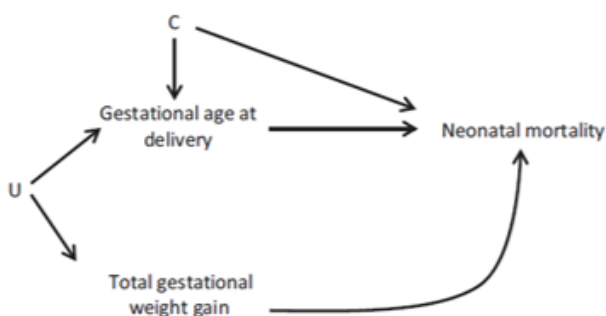
To overcome some of these limitations, studies have implemented a number of

approaches. To address the confounding bias created by gestational duration, the simplest

approach is to include gestational age in regression models where GWG is the main

exposure. Adjusting for gestational age in this way is advantageous in that it is simple

and easily interpretable. However, this method may not be beneficial in all scenarios. For

example, it is inappropriate to adjust for gestational age when the outcome of interest is

defined by gestational age (i.e., preterm birth), or when the outcome of interest is an

adverse event that only occurs during pregnancy (i.e., preeclampsia).[54] The adjustment of

gestational age in this situation may open any back door pathways (of exposure-mediator or mediator-outcome) that could introduce collider bias.[57,65]

When adjusting for gestational age is inappropriate, another way to reduce the confounding bias created by gestational duration is to calculate the average weekly rate of weight gain over the pregnancy. Often this is done by dividing the total GWG by the length of the pregnancy (weeks of gestation). While this does reduce the correlation between GWG and gestational age, it does not complete eliminate it.[57,66] This average weekly rate of weight gain also ignores the fact that weight gain throughout a pregnancy is not linear. The actual rate of weight gain during a pregnancy is often slower in the first trimester and can have varying inflection points depending on the woman's prepregnancy BMI.[67] It is also possible that this method can create an artificial relationship between low weight gain and the outcome of interest because pregnancies that are shorter in length will have artificially low rates of weight gain.[57]

A newer method for addressing the confounding bias caused by gestational age is by using z-scores for gestational age.[68] In this method the mean, standard deviation, and percentiles of weight gain across gestational weeks are calculated in a cohort of full-term pregnancies and according to their prepregnancy BMI category. The values in these charts (standardized pregnancy weight gain z-scores) are then used as a reference to compare a woman's total pregnancy weight gain to that of other pregnancies at similar gestational ages. This is done by calculating a weight gain z-score for each woman by subtracting the average week-specific weight gain from the reference charts from the observed total weight gain in the study and then dividing by the standard deviation of week-specific weight gain from the reference charts. The most common weight-gain for

gestational age z-scores charts used were developed by Hutcheon et al. in 2013[68] using a

cohort of women from the Magee-Women's Hospital in Pittsburth, PA who had

uncomplicated singleton pregnancies (n=648). This method is attractive because z-scores

should be uncorrelated with gestational age. Though the interpretability of the estimated

associations for weight gain z-scores are not intuitive, and there is an underlying

assumption that the weight gain in the study population is similar to the population used

to develop the weight gain z-score reference charts.[54]

One final approach to accounting for the correlation between gestational duration

and total GWG (single measure) is through time-to-event analyses (also known as

survival analyses).[69] A woman's weight gain at each gestational week is compared with

to other women's weight gain at the same gestation week and the hazard of adverse

pregnancy outcomes at each week are compared. A summary estimate is calculated to

determine if the rate of said event is different according to amount of weight gained while

pregnant (Cox-proportional hazard regression is commonly used).[69] This method

adequately addresses the correlation between gestational duration and GWG; however, it

may not be as practical in its implementation.[54] It requires a weight measurement each

week of pregnancy which is rarely available and is often interpolated, especially in the

case of single weight measurements. Commonly this is done by calculating the average

weekly rate of weight gain and has the same limitations with linearity as described above.

There are a few different approaches used to analyze serial weight measurements

that attempt to address the relationship between GWG and gestational duraiton. The first

is to calculate trimester-specific rates of weight gain during pregnancy. Doing so is very

similar to calculating the weekly rate of weight gain, but instead of a linear trend of the

whole pregnancy duration, a different trend is applied to each trimester. This allows

flexibility in the linear trend over the whole pregnancy (e.g., a flatter slope in the first

trimester and a steeper slope in the second and third trimesters), though each trimester-

specific rate does not include influences from the previous trimester.[54] This can limit the

value of this approach in describing the true trajectory of weight gain during pregnancy

and in its assumption of a linear trend within trimesters.

Another approach is to summarize the serial weight measurements using the area

under the curve (AUC).[70] All of a woman's weight measurements are plotted on a curve

with weight on the y-axis and gestational age on the x-axis. The area under this curve can

be calculated by connecting sequential weight measurement data points to create

trapezoids and then calculating the area of those trapezoids. The AUC is the sum of all

these trapezoids for all weight measurements for a specific woman. These AUCs can then

be compared and offer a simple-to-calculate method for summarizing serial weight

measurements. However, the resulting summary measure can be difficult to interpret and

since the AUC is highly dependent on gestational duration it may not be suitable for all

outcomes of interest, particularly ones that occur early in gestation.[54]

One final approach to using serial weight measurements is the use of multilevel

random effects models to model the weight gain during pregnancy.[71] Serial weight

measurements (and potentially other variables) are used to model weight gain (the

dependent variables) as a function of gestational age creating a smooth predicted

trajectory of weight gain at the individual-level for select periods during pregnancy

regardless other whether the pregnancy for a given individual reached each gestational

week. This predicted pattern of weight gain can then be used in regression models as

independent variable(s) to assess associations with the outcome(s) of interest. However, since this approach uses predicted instead of actual measurements of weight gain in the final models there is uncertainty around the weight gain measures that should be accounted for. Also, given the nature of the predicted pattern of weight gain, it can be difficult to determine the effect of weight gain at certain time periods during pregnancy.[54] The multilevel design addresses correlation of repeated measures of weight gain for each individual and the random effects allow each woman's starting weight and rate of weight gain to differ. These multilevel random effects models can also allow the shape of the weight gain trajectory to be nonlinear.

Childhood Asthma

There are also inconsistencies in the definition, collection, and analyses of the outcome of interest (childhood asthma). A commonly used asthma outcome is 'physician diagnosed asthma'. Asthma is difficult to diagnose because it shares symptoms with several other conditions (such as rhinitis and sinusitis), has diagnostic tests that can be difficult for children to preform reliably, especially those under the age of 5 years, and often requires physicians to rely on histories of symptoms which often lack detail, contain inaccuracies over long periods of time and can be inconsistent.[72] This can lead to some natural variation from physicians in the diagnosis of childhood asthma. However, physician asthma diagnoses can also be heavily dependent on the child's age, existing comorbidities, whether the parent(s) have asthma, and heightened awareness of the disease in recent years.[72] It is also common to use the child's symptoms to define asthma/wheeze outcomes. These can range widely from current symptoms, recent symptoms (a few weeks ago to a year ago), and/or any symptoms ever. Typically, these

symptoms are reported by parents which is subject to recall bias, especially over long periods of time. This can be particularly problematic if the parent's recall of symptoms is related to their child's exposure category or outcome status. Additionally, the same issues are present if parents are asked to recall a diagnosis from a physician or medication prescriptions. In analyses these outcomes are either presented separately or in combined categories (e.g., current asthma or wheeze), which can reduce the homogeneity within the outcome groups. While in an individual study these may not present a huge limitation, these inconsistencies make it difficult to compare across studies.

The ages of children currently included in studies of prepregnancy BMI, GWG, and childhood asthma varies widely between studies. Most studies do not include wide age ranges of children which can make comparison across studies difficult. Very few studies have followed children overtime to longitudinally to track their asthma symptoms/diagnoses. This limits the ability to assess and compare early childhood and late childhood asthma onset. Early onset of childhood asthma could result in more severe disease that may require different monitoring and/or treatment compared to later onset of childhood asthma.

Confounding

One of the main limitations of the current literature is that many confounding variables are not always included due to study constraints or design. Not only do these potential confounding factors have effects on the exposures (prepregnancy BMI and GWG) and outcome (childhood asthma) of interest, but they also commonly have effects on each other. These important potentially confounding variables include maternal characteristics (such as age, race/ethnicity, education, and smoking status), maternal

health conditions (chronic and gestational diabetes, chronic and gestational hypertension, and history of asthma/atopy), prenatal antibiotic use, parity, neonatal intensive care unit (NICU) admission and child's sex.

Maternal Age

Maternal age is typically considered an important confounder of the association between prepregnancy BMI, GWG, and childhood asthma. Maternal age is obtained through questionnaires or medical records and can be applied in analyses as a continuous measure or in categories (commonly 5- or 10-year increments). Overweight and obesity has been on the rise among women in the US in recent years, with the prevalence of overweight and obesity among adult (≥20 years old) women being 72% and 40% respectively.[73] Additionally, older women (≥40 years old) have a higher prevalence of obesity compared to younger women.[73] Studies have found significant associations between older women (≥35 years old) and higher prepregnancy BMI.[34,74]

While some associations between maternal age and GWG are inconsistent and unclear, the consensus is that an association exists. Some studies do not find a significant association between maternal age and GWG,[75] while other studies find that older women (≥35 years old) experience lower GWG[76,77] and that younger women (<35 years old) experience higher GWG.[76] The driving differences between these studies were the way maternal age was included in the analyses – studies that included maternal age in finer age categories (5 year increments) or continuously saw significant associations whereas studies that included wide age categories (10 year increments) saw insignificant associations.

Previous studies showed clear associations between children born to younger mothers (<21 years old) and an increased risk of childhood asthma,[34,78] however more recent studies have shown that children born to older mothers (≥35 years old) have an increased risk of childhood asthma.[79] While some of the directions and magnitudes of associations between maternal age, prepregnancy BMI, GWG, and childhood asthma are unclear, evidence persists that there is a relationship, and that maternal age should be treated as a confounder (Figure 1.4).

Figure 1.4 DAG highlighting confounding by maternal age
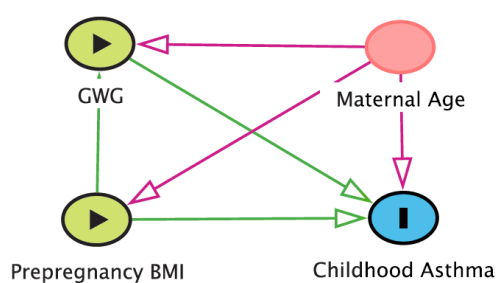
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Maternal Race & Ethnicity

Maternal race/ethnicity is a common confounder of the association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.5). Collection of race/ethnicity has been similar in most studies, which include categories of White, Black (African American), Asian, and Hispanic – though many studies include more. Similar to other maternal characteristics, race/ethnicity is often obtained from questionnaires or medical records. There is a known racial and ethnic disparity in adult obesity in the US, with non-Hispanic Black women having the highest prevalence of obesity (57%) –

significantly higher than Hispanic women (43.7%) and White women (40%).[81] Obesity

among all race/ethnicity categories has increased over the years, though the sharpest

increases have been seen among Hispanics.[82] Black mothers (compared to White

mothers) are more likely to gain excessive weight during pregnancy, while Hispanic

mothers are more likely to have inadequate amounts of weight gain.[83] Studies have also

demonstrated that Black and Hispanic mothers have increased risk of childhood asthma.[34]

Figure 1.5 DAG highlighting confounding by maternal race/ethnicity
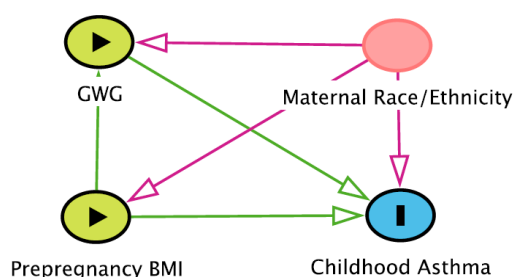
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Maternal Education

Maternal education is another common confounder of the association between

prepregnancy BMI, GWG, and childhood asthma (Figure 1.6). Maternal education is

often collected by questionnaires and can be used as a continuous variable (years of

education) or categories. The typical categories for maternal education include: less than

high school, high school graduate or GED, some college-no degree, Associate's degree,

Bachelor's degree, Advanced Degree, though sometimes the higher education categories

are combined due to smaller sample sizes. Many studies show that women with lower

levels of education have higher BMI's and are more likely to be obese compared to

women with higher education levels.[84] Many of these studies propose that these

relationships exist because women with lower education levels often have poorer diets

and more unhealthy habits (such as sedentary lifestyles) compared to women with higher

education levels. Similarly, studies seem to find a significant association between

maternal education and GWG with mothers who have lower education levels (high

school degree/GED or lower) gaining excessive amounts of weight gain.[75] There is also

evidence to suggest that higher levels of education are associated with reduced risk of

childhood asthma.[34,85] However, the strength of this association depends on how the

education categories are defined and there is no clear dose-response relationship.[85]

Figure 1.6 DAG highlighting confounding by maternal education

Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Maternal Smoking

Smoking before or during pregnancy can also be an important confounder to

consider when addressing the association between prepregnancy BMI, GWG, and

childhood asthma (Figure 1.7). Maternal smoking can be difficult to obtain with the use

of questionnaires or medical records – often missing or incomplete. While some studies

get detailed information about maternal smoking (like when mothers started and stopped

smoking or how much they were smoking) most studies simplify this information and

define maternal smoking as non-smokers (or never-smokers) and smokers (or ever-

smokers). Among adult women, those who smoke have significantly lower BMI's

compared to those that do not smoke or have never smoked.[86,87] Studies commonly

observe that smoking before or during pregnancy can lead to excessive weight gain

during pregnancy.[88] It is also well established that maternal smoking (before or during

pregnancy) can increase risk of childhood asthma.[88,89]

Figure 1.7 DAG highlighting confounding by maternal smoking

Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

*Diabetes*

Maternal conditions such as chronic and gestational diabetes are sometimes

included as confounders when estimating the association between prepregnancy BMI,

GWG, and childhood asthma (Figure 1.8). Chronic or gestational diabetes are often

measured as the presence or absence of the condition and is obtained through questionnaires or medical records. It is well known that obesity is considered a risk factor for chronic gestational diabetes. Many believe the pathway is through insulin resistance, which is increased in obese individuals and leads to the impairment of b-cell function which leads to diabetes development.[90,91] The relationship between weight gain and chronic diabetes is clear as a common side effect of taking insulin (prescribed to those with diabetes) is weight gain. However, the relationship between gestational diabetes and GWG is less clear. In the 2009 update to the IOM recommendations for GWG they noted a lack of evidence regarding the role of GWG in relation to gestational diabetes. However, after this update, some studies have shown that excessive GWG can be a risk factor for gestational diabetes.[92,93] Very few studies have been able to examine this relationship due to the timing of weight gain during pregnancy and gestational diabetes diagnosis and the fact that a diagnosis of gestational diabetes (and subsequent treatment) can affect GWG.

Previous studies that have investigated the effect of maternal diabetes on childhood asthma have reported inconsistent results (positive association,[33] or no association[27]), and did not differentiate between chronic diabetes and gestational diabetes. A more recent study that did specifically look at gestational diabetes, found no association with childhood asthma (all asthma: OR 1.12, 95% CI 0.88, 1.43).[46] Another recent study examined the effect of both chronic and gestational diabetes on bronchodilator dispensing (up to age 4 years) and found no association (diabetes: OR 0.93, 95% CI 0.71, 1.21; gestational diabetes: OR 0.97, 95% CI 0.71, 1.33).[89]

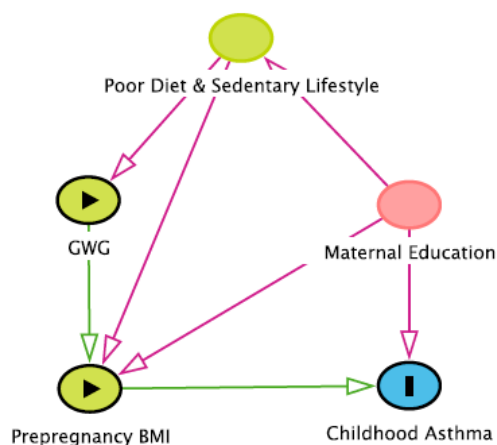Figure 1.8 DAG highlighting confounding by diabetes

Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Hypertension

Similar to diabetes, chronic and gestational hypertension are sometimes included as confounders when estimating the association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.9). Chronic or gestational hypertension is often measured as the presence or absence of the condition and is obtained through questionnaires or medical records. Studies suggest that prepregnancy BMI is a risk factor for hypertension (both chronic and gestational) and the relationship is linear, with risk of hypertension increasing as BMI increases.[94–96] There is also evidence to suggest that excessive weight gain during pregnancy is a risk factor for hypertension though this relationship has been sparsely studied.[97,98] Very few studies have examined the relationship between chronic or gestational hypertension and childhood asthma outcomes. Though, a recent study found no association (OR 0.98, 95% CI 0.54, 1.82) between chronic hypertension on bronchodilator dispensing up to age 4 years.[89]

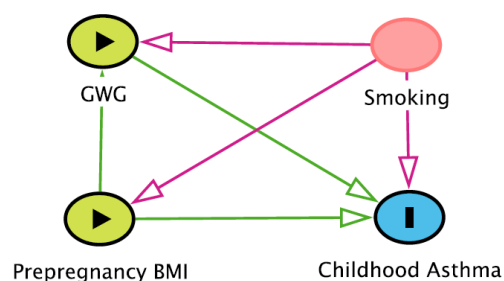Figure 1.9 DAG highlighting confounding by hypertension

Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Maternal History of Asthma and Atopy

There is some debate on whether maternal history of asthma or atopy should be considered as confounders of the association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.10). Often, maternal allergy or atopy is measured as the presence or absence of a mother's history of asthma or atopy obtained through questionnaires[30] or medical records.[89]

There is evidence to suggest that mothers who have asthma and/or atopy are more likely to gain excessive weight during pregnancy compared to mothers who do not.[89] These relationships can be supported by the connection between asthma, BMI, and weight gain[99] and known increases in risk for pregnancy complications (such as preterm birth, low birth weight babies, preeclampsia, and worsening asthma symptoms) among mothers with preexisting conditions like asthma and atopy.[100]

Preexisting conditions such as asthma and atopy in the mother also increases the risk of childhood asthma.[101,102] While the precise mechanisms behind these associations

are not well known, some suggest the inheritance of specific genes and in-utero exposures can contribute to these strong relationships.[102,103] Maternal asthma/atopy has also been shown to be a risk factor for childhood asthma.[103] Some mechanisms suggest that this association is driven by a pathway through childhood BMI – in that maternal asthma/atopy is associated with childhood obesity[88] and childhood obesity is associated with childhood asthma.[104]

For several years, studies have included maternal history of asthma and/or atopy as confounders, but rarely found that this changed the association between prepregnancy BMI, GWG, and childhood asthma.[103] In 2013, Leermakers et al.,[30] stratified their analysis of GWG and childhood asthma by maternal history of asthma or atopy and found that odds ratios for the association between GWG and childhood asthma were similar among children from mothers with a history of asthma or atopy compared to children from mothers without a history of asthma or atopy (OR 1.09 95% CI 1.01-1.17 vs OR 1.10, 95% CI 1.04-1.16). However, Leemakers et al.,[30] did find that prepregnancy BMI was associated with increased risk of childhood asthma only among children from mothers with a history of asthma or atopy (OR 1.07, 95% CI 1.00-1.15 vs OR 1.02, 95% CI 0.96-1.08).

Figure 1.10 DAG highlighting confounding by maternal asthma/atopy
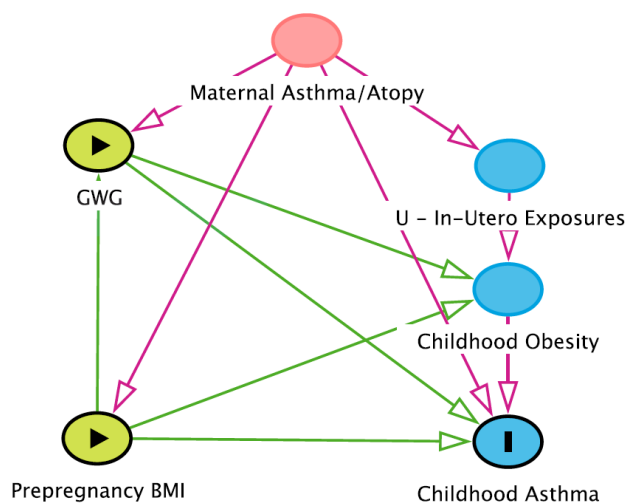
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
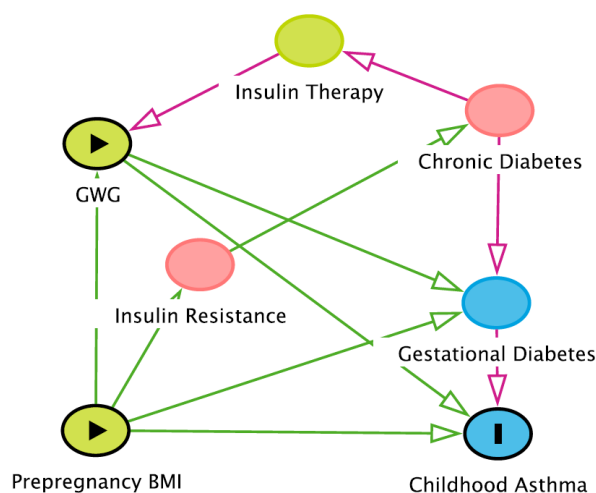Created using DAGitty[80]

Prenatal Antibiotic Use

Antibiotics are commonly used during pregnancy, though there are many considerations including type of antibiotic, timing of use, and dosages. Prenatal antibiotic use is commonly included as a confounder when examining the association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.11). Most often prenatal antibiotic use is obtained from medical records/dispensing records, though it can also be collected using questionnaires. In studies, prenatal antibiotic use is categorized by type of antibiotic, timing of use (i.e., first trimester, second trimester, etc.), and/or dosages (i.e., number of courses).

Since prenatal antibiotics are taken during pregnancy, they have no effect on prepregnancy BMI; additionally, there is no evidence to suggest that prepregnancy BMI could cause prenatal antibiotic use, though there may be a link between prepregnancy

antibiotic use and antibiotic use during pregnancy (such as a genetic predisposition to urinary tract infections).[105] A recent review summarized that most studies consistently find a link between antibiotic use and weight gain with effects present among adults and children and present over short or long periods of time.[106] The consensus is that antibiotic use alters the gut microbiota which plays an important role in a person's metabolism and the accumulation of fat.

There is also a general consensus that prenatal antibiotic use increases the risk of childhood asthma. A systematic review found an increased risk of childhood asthma with any antibiotic use during pregnancy (pooled OR: 1.24, 95% CI: 1.02, 1.50), though this only included three studies at the time.[107] More recent studies have found increases in risk of childhood asthma among mother's who had any exposure to antibiotics during their pregnancies (adjusted hazard ratio [HR]: 1.10, 95% CI: 1.00, 1.12)[105]; one finding that risk increased according to timing of antibiotic use (first trimester adjusted OR: 1.23, 95% CI: 1.08, 1.41, second trimester adjusted OR: 1.30, 95% CI: 1.15, 1.47, third trimester adjusted OR: 1.40, 95% CI: 1.25, 1.57).[108]

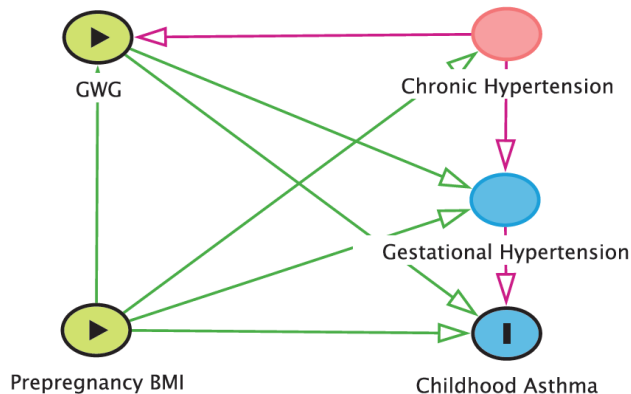Figure 1.11 DAG highlighting confounding by prenatal antibiotic use
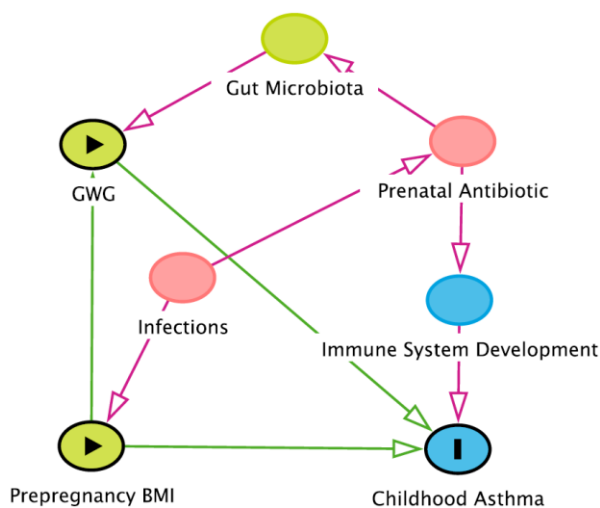
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Parity

Parity is another important confounder to consider when addressing the

association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.12).

Parity is collected through medical records or questionnaires and is commonly

categorized as first-born, second-born, and third-born and above, or more simply as first-

born vs second-born and above. There is some evidence to suggest that multiparous

women are more likely to have a higher prepregnancy BMI than nulliparous or

primiparous women,[109] though some studies see that this association is dependent on

prepregnancy BMI, number of births, and race/ethnicity.[110]

It is less clear if there is an association between parity and GWG. A recent

systematic review of 33 studies that examined the association between parity and GWG

found inconsistent results: 14 studies found that primiparous women compared to

multiparous women were more likely to gain more weight or experience excessive weight gain during pregnancy, while 10 studies found that multiparous women, compared to primiparous women, were more likely to gain more weight or gain excessive weight during pregnancy.[109] The other 9 studies did not report a significant association between parity and gestational weight gain.[109] The resulting meta-analysis of 17 of these studies showed a pooled weighted average effect that was insignificant (r=0.04, 95% CI: -0.10, 0.16).

The literature is also less clear on the relationship between parity and childhood asthma. A review published in 2002 summarized 31 studies that estimated this association and found 22 of them reported an inverse association (childhood asthma risk decreased with increasing family size, though not all were significant), while 6 of them reported no association at all, and 3 studies found a positive association, though only one was significant.[111] Somewhat more recent studies are still inconsistent with one reporting several null associations between asthma and parity[112] and another reporting a negative association.[113]

Figure 1.12 DAG highlighting confounding by parity

Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

NICU admission

When information on NICU admission is available, most studies will include it as a confounder of the association prepregnancy BMI, GWG, and childhood asthma (Figure 1.13). NICU admission information is obtained from medical records or sometimes from questionnaires and is typically considered as a binary variable (yes or no). Of the few older studies that have assessed maternal prepregnancy BMI, GWG, and NICU admission, they agree that having a normal BMI and gaining the recommended amount of weight during pregnancy lowers the risk of NICU admission.[114] However, it is likely that this relationship is indirect, through a pathway of premature birth, which is a major risk factor for NICU admission. Among these studies there is a growing consensus that the risk of preterm birth (and NICU admission) is higher among women with a prepregnancy BMI of overweight and obese (compared to underweight and normal weight women) and those that gain inadequate or excessive amounts of weight during pregnancy.[114–117] These studies also suggest that the strength and direction of the association may vary depending on the subtype of preterm birth (e.g., premature rupture of membrane or indicated preterm). The mechanism(s) through which prepregnancy BMI and GWG are associated with preterm birth is still largely debated, though there are some theories. The main one suggests that inflammation related to obesity is responsible for the association reported between obesity and preterm birth[116,118]; inflammation is also associated with excessive GWG.[23]

The association between NICU admission and childhood asthma is also likely an indirect one. It could be due to NICU related lung injuries that result in increased airway

reactivity or shared susceptibilities to prematurity. One possible mechanism is through chronic lung disease of prematurity (or bronchopulmonary dysplasia [BPD]), which is highly correlated with both NICU admission and childhood asthma.[119,120] Studies report that infants discharged from the NICU diagnosed with BPD are more likely to need respiratory medications and supplemental oxygen, experience wheezing and/or altered pulmonary functions and be diagnosed with asthma later in life. [119,120]

Figure 1.13 DAG highlighting confounding by NICU admission

Abbreviations: GWG – gestational weight gain, BMI – body mass index, NICU – neonatal intensive care unit, BPD – bronchopulmonary dysplasia
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Child's Sex

Child's sex is sometimes considered a confounder of the association between prepregnancy BMI, GWG, and childhood asthma (Figure 1.14). This information is collected from medical records or through questionnaires and is categorized as males versus females. The relationship between child's sex, prepregnancy BMI, and GWG is not well studied but there are some theories regarding mechanisms. Prepregnancy BMI

and child's sex could be linked through common effects on birthweight; and GWG and child's sex could be linked through mutual effects on fetal growth patterns.[121,122]

Of greater interest, is the relationship between a child's sex and childhood asthma. Asthma diagnoses are higher among boys compared to girls before puberty and higher among girls compared to boys after.[123] Many think that young boys have a higher asthma prevalence due to sex differences in airway size, immunology, and lung growth, and that, after puberty, sex hormone changes contribute to the higher prevalence among girls.[123]

Two studies have looked at effect modification by child's sex on the association between gestational weight gain, prepregnancy BMI, and childhood asthma. The first found that children of obese mothers (aged 6-12 years) had an increased risk for inhaled corticosteroid use, and this effect was larger for girls than for boys (girls OR=1.52, 95% CI:1.34, 1.72; boys OR=1.20, 95% CI: 1.08, 1.34).[124] Among children aged 13-16 years, this association was similar direction for girls (OR=1.28, 95% CI: 1.07, 1.53), but changed and became nonsignificant for boys (OR=1.05, 95% CI: 0.87, 1.26). The second study found no effect modification by child's sex on prepregnancy BMI or gestational weight gain and any asthma among all children (ages ranging from <6-17.9 years).[46] Due to this changing trend in childhood asthma prevalence among boys and girls it is important to consider that the effect of prepregnancy BMI and GWG on childhood asthma could be affected by child's sex.

Figure 1.14 DAG highlighting confounding by child's sex
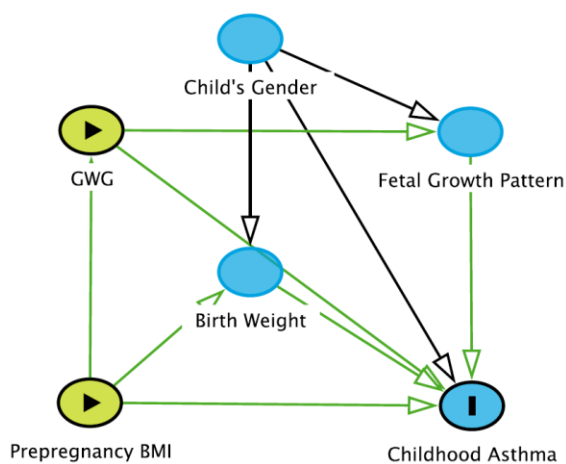
Abbreviations: GWG – gestational weight gain, BMI – body mass index
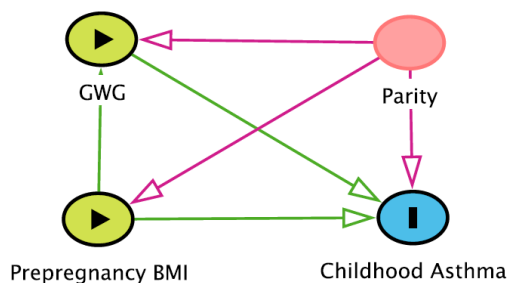Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Mediators

Cesarean Delivery

Commonly, cesarean delivery is controlled for in analyzes even though it could be on the causal pathway between prepregnancy BMI, GWG, and childhood asthma. Cesarean delivery is collected from medical records or questionnaires and can also be referred to as 'mode of delivery.' Maternal obesity is a known risk factor for cesarean delivery[125] and the risk of cesarean delivery has been shown to increase as prepregnancy BMI increases.[126] A recent study also shows that prepregnancy BMI was associated with cesarean delivery complications.[127] Many studies also report an increased risk of cesarean delivery for those that gain excessive weight during their pregnancy.[128–130] One study has reported both individual and joint effects for prepregnancy BMI and GWG on cesarean delivery.[131] It has also been established that cesarean delivery is a risk factor for childhood asthma[132] and that this association persists for elective and emergency cesarean

deliveries.[133] This association is thought to exist due to the absence of exposure to vaginal flora which can affect immune development.[134] Despite the evidence that suggests cesarean delivery could be on the causal pathway between prepregnancy BMI, GWG, and childhood asthma, the few studies that have investigated this have found no mediating effect of cesarean delivery.[46]

Figure 1.15 DAG highlighting mediation by cesarean section
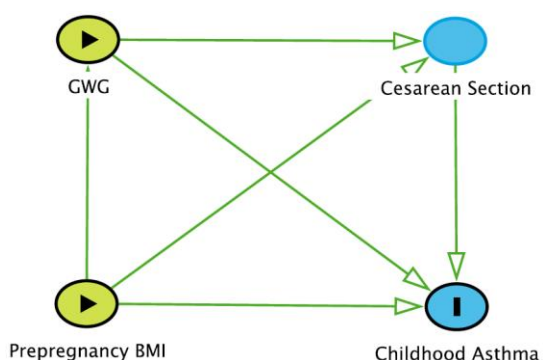
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
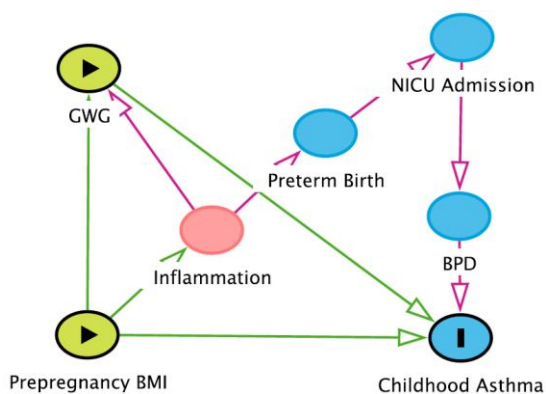Created using DAGitty[80]

Child's BMI

Child's BMI is another important factor to consider as an intermediate between prepregnancy BMI, GWG, and childhood asthma (Figure 1.16). Child's BMI is rarely included in studies of this specific association due to sparse collection and inconsistent timing of measurement and asthma diagnoses; when included it is typically obtained from medical records. There is strong evidence linking prepregnancy BMI to childhood obesity, with a recent meta-analysis reporting a 264% increase in odds of childhood obesity among children born to mothers who were obese.[135] While a consensus exists that

obesity among children has many dynamic causes (including physiological, environmental, social and behavioral) there is also some evidence that in-utero epigenetic processes that affect DNA and the gut microbiome could contribute to childhood obesity.[136] There is also evidence to suggest that excessive GWG can increase risk for childhood obesity, with some of the stronger effects found among older children (aged 10 years and older).[137] This could be explained by intra-uterine programming mechanisms which can become more apparent later in life, and fetal over-nutrition which can permanently alter function of adipose tissue, metabolism, and appetite regulation.[20] While independently prepregnancy BMI and GWG are strongly associated with childhood BMI the joint impact is not.[137]

Childhood obesity and childhood asthma have been widely studied and while many studies find a consistent link some have difficulty establishing which condition came first. In some cases, obesity and asthma are diagnosed together and there are many possible mechanisms linking the two conditions.[138] Though several recent studies have evaluated longitudinal data and found that increased BMI among children does increase the risk of developing incident childhood asthma.[139–141] The main mechanisms thought to influence this relationship are similar to those for adults: inflammation and reduced lung function related to obesity.[138] It is also possible that sex difference exists in the association of obesity and asthma among children.[142]

Though child BMI appears to be an important potential mediating factor of the relationship between prepregnancy BMI, GWG, and childhood asthma, only two studies to date have formally investigated this. One study found that prepregnancy BMI increased the risk of childhood asthma (adjusted RR=2.32, 95% CI: 1.49, 3.61) and

wheezing (adjusted RR=2.16, 95% CI: 1.28, 3.64); and that child's BMI did have a

mediating effect on the association between prepregnancy BMI and wheezing, but not

prepregnancy BMI and asthma.[45] The other only found weak evidence supporting a

mediating effect of child's BMI.[44]

Figure 1.16 DAG highlighting mediation by child's BMI
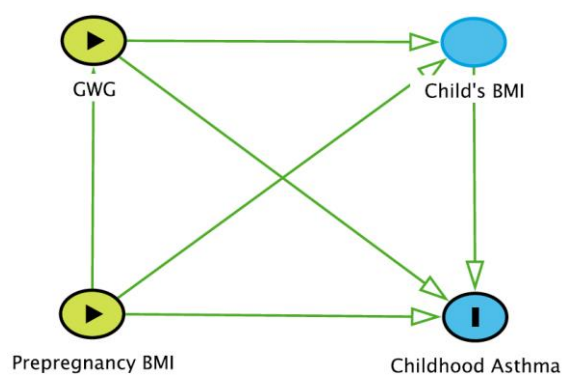
Abbreviations: GWG – gestational weight gain, BMI – body mass index
Legend: green arrow – causal pathways, pink arrow – biasing pathway
Created using DAGitty[80]

Opportunities for Contribution

Since the literature is inconsistent and, in some cases, sparse on this topic, more

research is needed. Future studies should focus on collecting data or choosing data

sources that allow inclusion of more potential confounders as previous research was

limited in the potential confounders they were able to include. The same can be said for

potential mediators. In many previous studies childhood asthma was assessed at one point

in time for one age group; multiple ages could be assessed and included to investigate

these associations throughout childhood. These previous studies do not include the newer

subcategories of obesity (i.e., obesity classes 1, 2 & 3). It could be important to consider

that women previously grouped together may have different relationships with important

variables in the study depending on their finer category of obesity. Each study to date has

characterized total GWG in a different way, which can make comparison of these studies

difficult. Investigating more dynamic ways to characterize GWG as an exposure could

help determine its role in these associations. For example, the characterization and

analysis of GWG could include repeated weight measurements not just total weight gain,

or GWG can be modeled non-linearly in the analysis. Additionally, considering the

relationship between GWG and prepregnancy BMI, when GWG is the main exposure of

interest, the results should be stratified by prepregnancy BMI. This can help eliminate

confounding between BMI classes and potentially highlight specific recommendations

for each BMI class. And finally, the relationship between prepregnancy BMI, GWG, and

gestational age is mostly missing from current literature. This is an important relationship

to consider as it can lead to biased estimates.

Specific Aims

The United States has seen an 11% increase in the prevalence of prepregnancy

obesity from 2016-2019 (26.1% in 2016 to 29.0% in 2019). Prepregnancy obesity can

impact the intrauterine environment thus affecting fetal development and the health of the

child later in life. Many studies already suggest that maternal obesity increases the risk of

childhood asthma, though these studies do not take into account the impact of gestational

weight gain (GWG) on child's asthma risk. There are few studies that have investigated

the association between GWG and childhood asthma. Results vary widely among these

studies and there is no consensus on how to best characterize GWG for analysis.

Additionally, important biasing pathways are not considered in the current literature,

specifically, the role of gestational age and its association with prepregnancy BMI, GWG and childhood asthma. If these methodological challenges are not properly addressed estimated associations may be biased.

The long-term goal is to add to the knowledge base on prepregnancy BMI, GWG, and childhood asthma and to inform recommendations. The last time recommendations on ideal ranges of weight gain during pregnancy were updated was 2009. Since the literature presents mixed results, this research's overall objective is to determine if prepregnancy BMI and GWG affect the risk of childhood asthma. This research will attempt to address several methodological challenges using electronic medical records, analyses informed by directed acyclic graphs (DAGs), and sensitivity analyses to help highlight potential biases.

Aim 1: To estimate the association between prepregnancy BMI and child's asthma risk for different follow-up ages. Hypothesis: Prepregnancy obesity will be associated with higher risk of childhood asthma. Using electronic medical record data from mother-child pairs, the association will be estimated while controlling for GWG, gestational age, and child's BMI. These results will contribute to the literature based on prepregnancy BMI and childhood asthma using a robust study design that considers the complex relationship between gestational age, the exposure, and the outcome.

Aim 2: To investigate the role of potential mediating factors in the association between prepregnancy BMI and child's asthma risk for different follow-up ages. Hypothesis: The associations between prepregnancy BMI and childhood asthma are partly mediated through child's own BMI, GWG or gestational age. Using electronic medical record data from mother-child pairs, potential mediator(s) will be evaluated.

These results will contribute to the literature based on prepregnancy BMI and childhood asthma using a robust study design that considers the complex relationship between these factors.

Aim 3: To estimate the association between GWG and child's asthma risk for different follow-up ages. Hypothesis: Higher GWG will be associated with higher risk of childhood asthma. Using electronic medical record data from mother-child pairs, the association will be estimated while stratifying by prepregnancy BMI and controlling for gestational age. These results will contribute to the literature based on GWG and childhood asthma using a robust study design that considers the complex relationship between gestational age, the exposure, and the outcome.

Prepregnancy obesity is on the rise in the United States. These increasing trends bring a need for further understanding of the potential effects prepregnancy obesity has on childhood asthma risk. An additional risk factor for child's asthma is GWG and recommendations for ideal weight gain during pregnancy have not been updated since 2009. A better understanding of the unbiased association between prepregnancy BMI, GWG, and childhood asthma is essential to inform future recommendations and policy.

Chapter 2: 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 dispensings. 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.

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 effecting 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 assessment of obese subclasses, for which there is little data available to address the association with childhood asthma.

Methods

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 January 1, 2005, and January 1, 2014; follow-up was included through January 1, 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., non-continuous 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.

Measures

Exposure: Prepregnancy BMI

Prepregnancy 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 after.

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

Outcome: Child's asthma

Asthma was defined using a combination of International Classification of Disease (ICD) diagnosis codes and asthma-related prescription medication dispensings. 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-9 493 or ICD-10 J45) at least thirty days apart and (2) two controller medication dispenses at least thirty days apart, with at least one within twelve 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 twelve 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.

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 (S5.1)

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 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 DAGitty[18]) in Figure 2 shows an example of how some covariates could be considered both confounders (though backdoor pathways) and/or intermediates (on the pathway) between prepregnancy BMI and child's asthma (full DAG in Figure S1). For example, prepregnancy 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 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).

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 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 (Table 2 & Table S2). Table 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 (prepregnancy and gestational), hypertension (chronic and gestational), prenatal antibiotics, and caesarean 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 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 final adjusted models (results excluding these covariates from models presented in Figure 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 to 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 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/m^2 (i.e., RR=1 at BMI=22 kg/m^2). Among children in the age 4 cohort there was a general trend of increasing asthma risk as prepregnancy BMI increased from 18-30 kg/m^2. In the age 6 cohort asthma risk increased as prepregnancy BMI increased from BMI values of 20-35 kg/m^2, 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).

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 non-significant, 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 association[29] 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/m^2) increase in prepregnancy BMI (OR=1.03, 95% CI=1.02, 1.03).[5] Compared to 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 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 S5.3).

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 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]

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 evidence[21] 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 mediation dispensings. Additionally, using EMR data

ensured accuracy of events at birth (delivery method and birth weight), and allowed for

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 sub-classes, 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 dispensings. 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 though 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, final models adjusted

for these covariates (results without adjusting for these covariates are presented in Figure 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 is a strength of this study but represents 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 (prepregnancy BMI calculated from height and weight measurements); however, missing exposure was unrelated to any study variables except birth year reflecting 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 obesity[3] 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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Figure 2.1: Follow-up flow chart
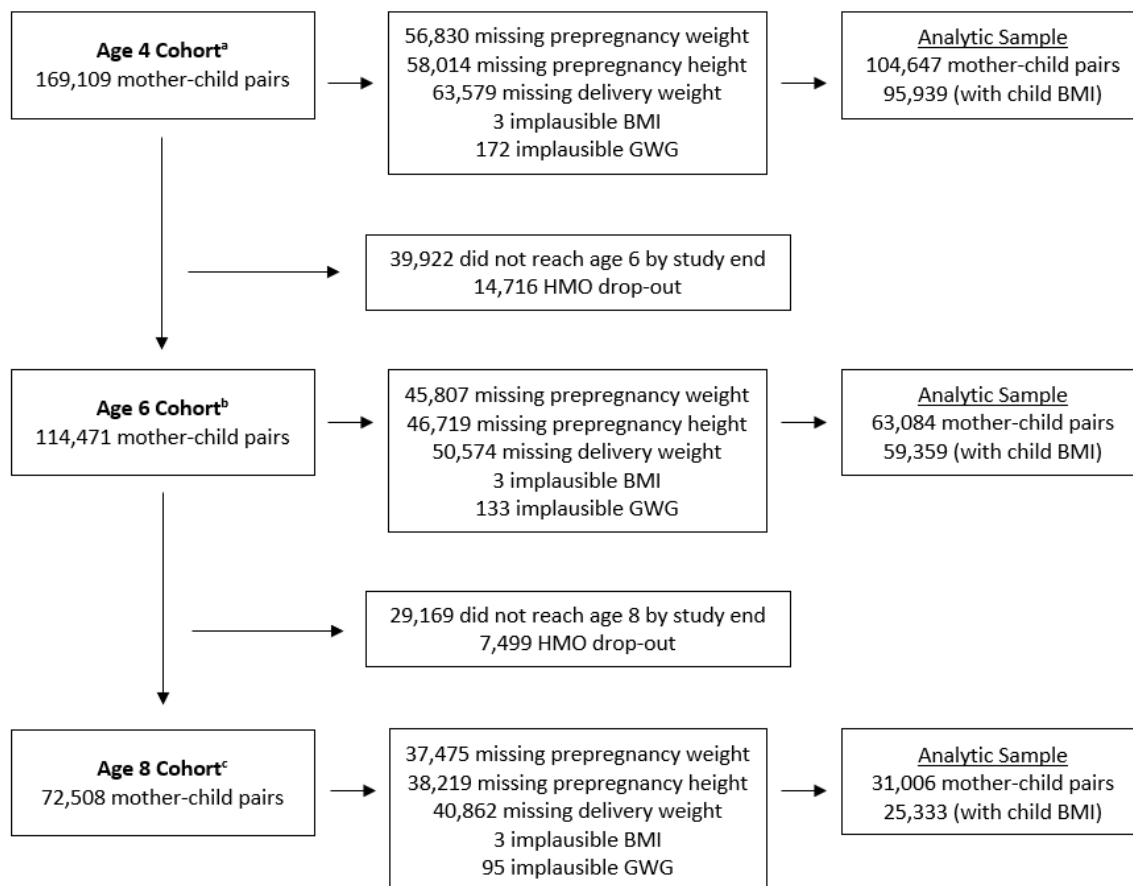
Abbreviations: BMI – body mass index, GWG- gestational weight gain, HMO – health maintenance organization
[a]covers births from 1/1/2005 – 1/1/2014
[b]covers births from 1/1/2005 – 1/1/2012
[c]covers births from 1/1/2005 – 1/1/2010
Notes: Some mother-child pairs were missing more than one measurement. BMI <12 kg/m^2 or >81 kg/m^2 and GWG $<$-40 lbs or >100 lbs were considered implausible. Most prepregnancy anthropometric measures were missing due to incremental adoption of electronic medical records and women enrolling mid-pregnancy. Exposure (prepregnancy BMI calculated from height and weight measurements) missingness was independent of all variables except birth year.

Figure 2.2: Directed acyclic graph of maternal prepregnancy BMI and child's asthma showing confounding and mediation pathways through child's BMI
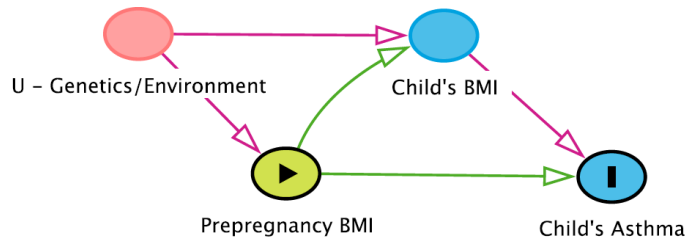
Abbreviations: BMI – body mass index
Legend:
Exposure = prepregnancy BMI
Outcome = child's asthma
Green arrow = causal pathway
Pink arrow = biasing pathways

Table 2.1: Child characteristics for follow-up ages 4, 6, and 8

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	5251 (5.0)	104467	4729 (7.5)	63084	2518 (8.1)	31006
Infant Sex						
Male	3352 (6.3)	53309	2975 (9.2)	32178	1566 (9.9)	15881
Female	1899 (3.7)	51158	1754 (5.7)	30906	952 (6.3)	15125
Birth Weight						
<2500g	390 (8.8)	4440	327 (12.5)	2612	162 (13.0)	1246
2500-4000g	4284 (4.9)	88055	3866 (7.3)	53175	2061 (7.9)	26016
>4000g	577 (4.8)	11972	536 (7.3)	7297	295 (7.9)	3744
Parity						
First Born	2187 (4.9)	45034	1999 (7.4)	26938	1062 (8.1)	13040
Second Born	2020 (5.3)	38092	1788 (7.7)	23081	945 (8.3)	11388
Third Born +	1044 (4.9)	21341	942 (7.2)	13065	511 (7.8)	6578
NICU Admission						
Yes	585 (8.4)	6937	513 (12.0)	4260	266 (12.5)	2127
No	4666 (4.8)	97530	4216 (7.2)	58824	2252 (7.8)	28879
First Year Antibiotics						
Yes	3199 (8.1)	39719	2706 (10.7)	25194	1435 (11.1)	12898
No	2052 (3.2)	64748	2023 (5.3)	37890	1083 (6.0)	18108
Child BMI[a] (pct)						
Underweight (<5th)	248 (5.3)	4698	174 (7.4)	2339	78 (8.3)	941
Normal (5th-84th)	3434 (5.0)	69169	2936 (7.1)	41353	1508 (8.5)	17676
Overweight (85th-95th)	828 (5.9)	13975	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: NICU – neonatal intensive care unit, BMI – body mass index
[a]Child BMI percentiles calculated using height and weight measurements within 6 months of previous birthday

Table 2.2: Maternal characteristics for follow-up ages 4, 6 and 8

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	5251 (5.0)	104467	4729 (7.5)	63084	2518 (8.1)	31006
Prepregnancy BMI[a]						
Underweight	104 (4.1)	2528	97 (6.5)	1500	54 (7.0)	771
Normal	2339 (4.5)	51845	2078 (6.6)	31402	1130 (7.3)	15427
Overweight	1476 (5.2)	28153	1329 (7.9)	16896	695 (8.4)	8266
Obese 1	747 (5.8)	12902	684 (8.7)	7821	348 (9.0)	3870
Obese 2&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)	43201	2246 (8.4)	26723	1240 (9.1)	13625
16+	2611 (4.6)	56571	2225 (6.6)	33477	1138 (7.2)	15910
Missing	77 (7.4)	1035	54 (9.8)	551	24 (10.4)	231
Race/Ethnicity						
White	1868 (4.1)	45446	1629 (6.0)	27372	865 (6.4)	13519
Black	498 (8.4)	5923	422 (11.7)	3611	245 (13.3)	1841
API	1492 (5.1)	29274	1394 (8.0)	17532	713 (8.4)	8501
Hispanic	1352 (5.8)	23133	1258 (8.9)	14192	691 (9.9)	7000
Other/Missing	41 (5.9)	691	26 (6.9)	377	4 (2.8)	145
Asthma[b]						
Active	1186 (9.0)	13246	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)	84328	3218 (6.3)	51154	1740 (6.9)	25190
Allergies[c]						
Yes	3190 (6.1)	52237	2995 (9.1)	32852	1641 (9.8)	16720
No	2061 (3.9)	52230	1734 (5.7)	30232	877 (6.1)	14286
Smoking During Pregnancy						
Yes	521 (5.4)	9573	430 (8.0)	5404	213 (8.6)	2491
No	4730 (5.0)	94894	4299 (7.5)	57680	2305 (8.1)	28515
Prepregnancy Diabetes						
Yes	153 (7.1)	2167	137 (10.2)	1337	81 (11.8)	688
No	5098 (5.0)	102300	4592 (7.4)	61747	2437 (8.0)	30318
Gestational Diabetes						
Yes	742 (5.4)	13832	672 (8.2)	8197	350 (9.6)	3648
No	4509 (5.0)	90635	4057 (7.4)	54887	2168 (7.9)	27358
Chronic Hypertension						
Yes	241 (6.4)	3754	246 (9.8)	2498	138 (10.9)	1270
No	5010 (5.0)	100713	4483 (7.4)	60586	2380 (8.0)	29736
Gestational Hypertension						
Yes	722 (6.0)	11961	639 (8.9)	7220	336 (10.0)	3370
No	4529 (4.9)	92506	4090 (7.3)	55864	2182 (7.9)	27636
Breastfeeding						
<3mo	1375 (5.6)	24457	1180 (7.7)	15297	647 (8.5)	7625
3-6mo	847 (5.8)	14660	760 (8.3)	9126	379 (8.7)	4351
>6mo	2576 (4.5)	57576	2369 (7.0)	33770	1248 (7.6)	16414
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)	29991	1681 (9.1)	18407	922 (10.1)	9158
No	3379 (4.5)	74476	3048 (6.8)	44677	1596 (7.3)	21848
Caesarean Section						
Yes	1633 (5.8)	27971	1499 (8.8)	17016	810 (9.6)	8414
No	3618 (4.7)	76496	3230 (7.0)	46068	1708 (7.6)	22592
Total GWG[d]						
Inadequate	1120 (5.2)	21520	921 (7.3)	12652	486 (7.9)	6147
Adequate	1630 (4.8)	34164	1486 (7.2)	20748	788 (7.7)	10186
Excessive	2501 (2.1)	48783	2322 (7.8)	29684	1244 (8.5)	14673
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

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30 – 34.9 kg/m^2), obese class 2/3 (35+ kg/m^2)

[b]Asthma during this pregnancy determined using diagnoses reported on medical intake forms and medication dispensing

[c]Maternal allergies including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the electronic medical record

[d]Calculated as delivery weight minus prepregnancy weight; based on Institutes of Medicine recommend weight gain per prepregnancy BMI category

Figure 2.3: Adjusted risk ratios for prepregnancy BMI category (relative to Normal) and
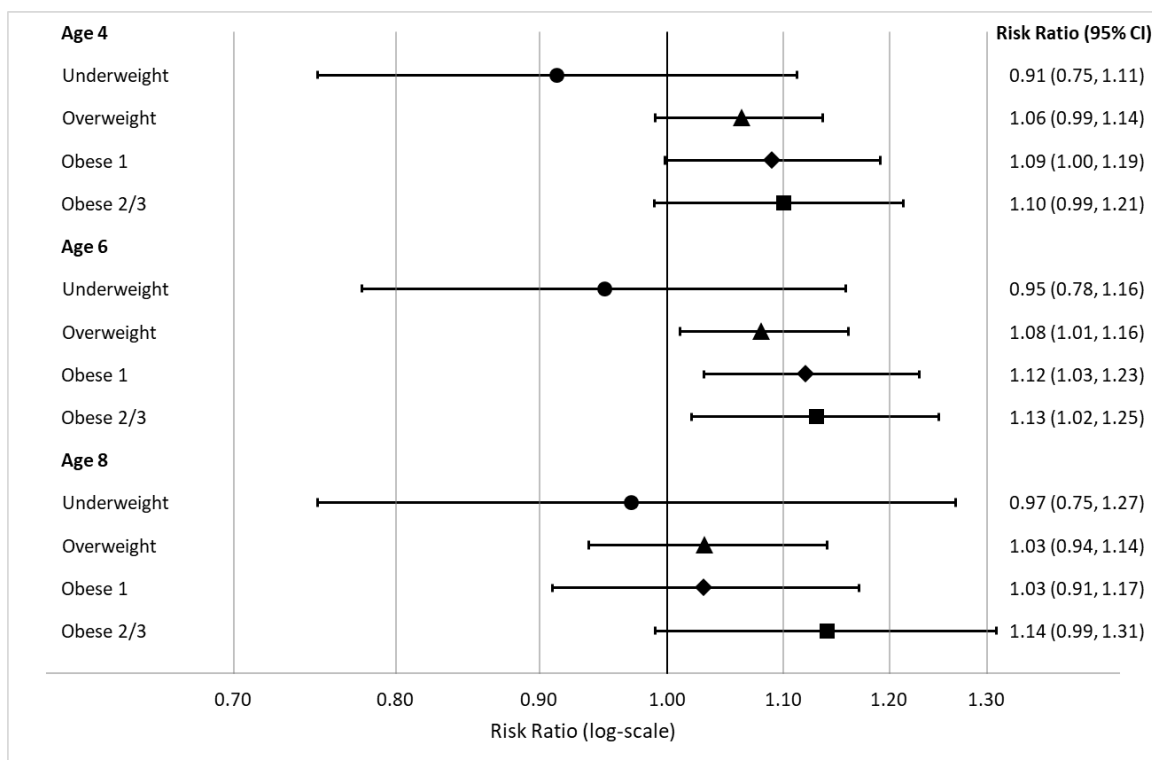
child's asthma, for follow-up ages 4, 6, and 8

Abbreviations: BMI – body mass index
Notes: 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.

Figure 2.4: Adjusted risk ratios for continuous BMI (spline) and child's asthma, for

follow-up ages 4, 6, and 8
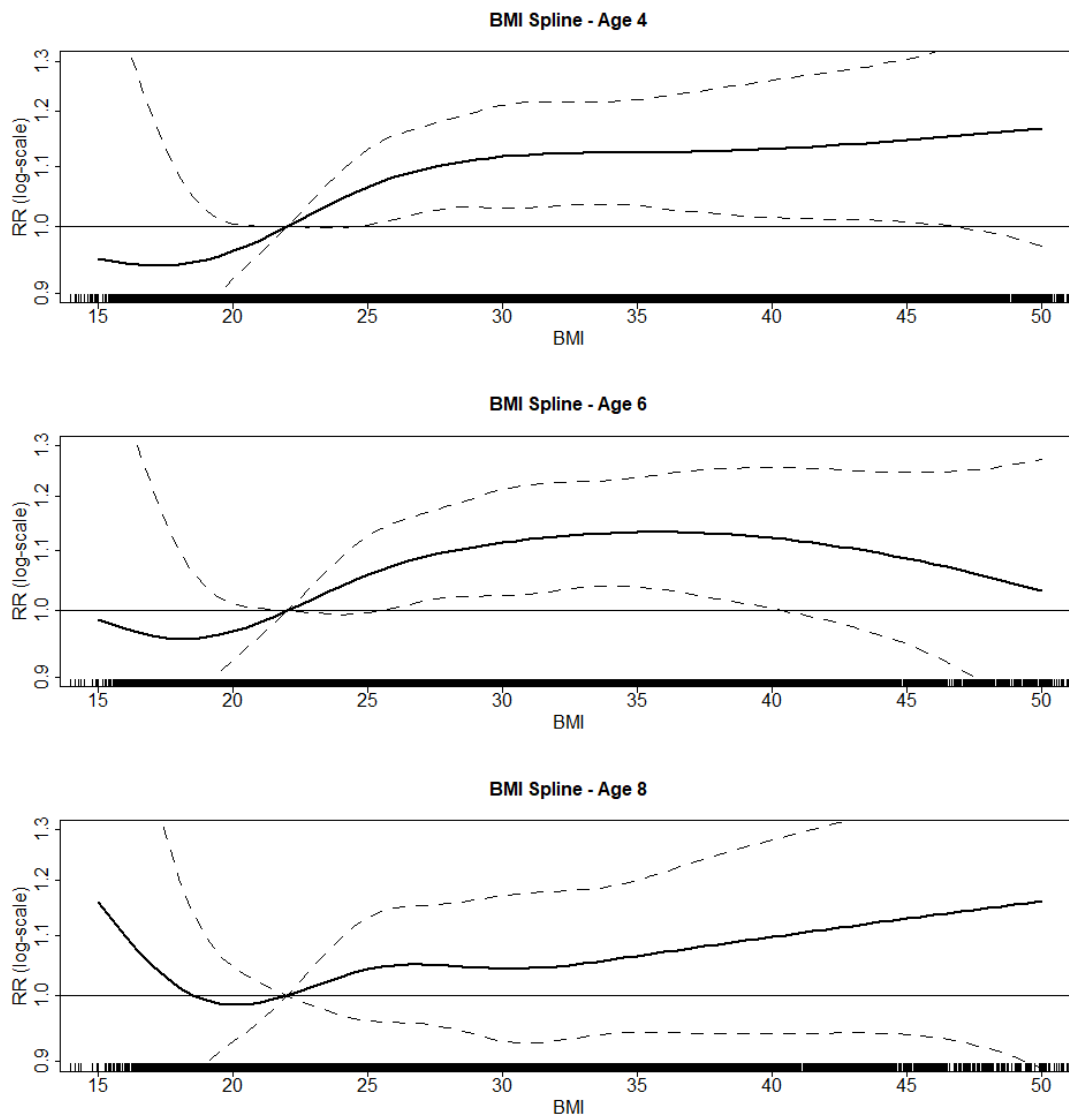
Abbreviations: RR – risk ratio, BMI – body mass index
Notes: All models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI. Risk ratios are presented relative to a reference of BMI=22 kg/m^2. Rug is presented along the x-axis of each graph to show distribution of data.

Chapter 3: Maternal Obesity and Childhood Asthma Risk: Exploring Mediating Pathways

Abstract

Background: Growing evidence for an effect of maternal obesity on childhood asthma motivates investigation of mediating pathways. We aim to investigate childhood BMI, gestational weight gain (GWG), and gestational age (GA) as potential mediators of this association.

Methods: We used electronic medical records from mother-child pairs enrolled in Kaiser Permanente Northern California integrated healthcare system. Cohorts of children were followed from their birth (in 2005-2014) until age 4 (n=95,723), 6 (n=59,230), or 8 (n=25,261). Childhood asthma diagnosis at each age was determined using ICD codes and medication dispensings. Prepregnancy BMI (underweight [<18.5], normal [18.5-24.9], overweight [25-29.9], obese [≥30]) and child's BMI (BMI-for-age percentiles: underweight [<5th], normal [5th-85th], overweight [85th-95th], obese [>95th]) were obtained using anthropomorphic measurements. GWG (delivery weight minus prepregnancy weight) was categorized based on Institutes of Medicine recommendations (inadequate, adequate, excessive). GA was defined as pregnancy duration in weeks. Implementing first causal inference test (CIT) then causal mediator models, we examined the potential mediating effect of childhood BMI, GWG, and GA on the association between prepregnancy BMI and childhood asthma.

Results: Overall, risk of childhood asthma increased as prepregnancy BMI increased (age 4 risk ratio: 1.07, 95% confidence interval [CI]: 1.04, 1.09, per 5 kg/m^2 increase in BMI.

CIT identified childhood BMI and GA, but not GWG as potential mediators. Causal mediation models confirmed childhood BMI as having a partial mediating effect, but showed limited evidence for GA.

Conclusions: Childhood overweight/obesity does have a modest mediating effect on the association between prepregnancy BMI and childhood asthma.

Introduction

Asthma is the most common chronic disease among children in the United States (US) and has been increasing over the past decade.[1] Recent increases in obesity have also been reported, especially increases in maternal prepregnancy obesity.[2] There is growing evidence linking prepregnancy obesity to childhood asthma development, though the biological mechanisms are unclear.[3,4] Prepregnancy obesity may increase childhood asthma risk through intrauterine environment changes due to chronic inflammation that affects fetal growth, specifically during important phases of immunological development.[5,6]

Mediating pathways between prepregnancy obesity and childhood asthma have been sparsely studied. Of particular interest are child's body mass index (BMI), gestational weight gain (GWG) and gestational age (GA), as these factors could lie on the causal pathway between prepregnancy obesity and childhood asthma. The literature shows strong evidence connecting maternal obesity to childhood obesity,[7] as well as a consistent link between childhood obesity and childhood asthma.[8] Prepregnancy BMI has a known association with preterm birth (i.e., GA <37 weeks), though the exact role is undefined.[9] Additionally, preterm birth is a known risk factor for childhood asthma.[10] Total GWG is inversely associated with prepregnancy BMI (in that women with higher

prepregnancy BMIs tend to gain less during pregnancy).[11] And inadequate or excessive GWG has been found to significantly increase risk of childhood asthma.[4] A few studies have included some measures of childhood obesity while investigating the association between prepregnancy obesity and childhood asthma, though they report mixed conclusions.[12–18] Only two studies have included GA as a potential mediator, and they reported no evidence of mediation.[13,16] To our knowledge, no study has identified or evaluated GWG as a potential mediator between prepregnancy obesity and childhood asthma.

Additional investigations into the potential mediating effect these three factors may have on the association between prepregnancy obesity and childhood asthma could provide new insights to underlying biological mechanisms. In this study we apply formal mediation analysis techniques – the causal inference test (CIT)[19] and causal mediator models[20] – to assess the presence and magnitude of the potential mediating effects of childhood BMI, GWG, and GA. We use electronic medical record (EMR) data from a large health maintenance organization to provide objective measures of prepregnancy BMI, potential mediators, and childhood asthma outcomes at multiple follow-up ages.

Methods

Study Population

Kaiser Permanente Northern California (KPNC) is an integrated healthcare system serving as both insurer and healthcare provider for its members. We included singleton mother-child pairs who were enrolled in KPNC throughout pregnancy and gave birth between 2005-2014. Continuous enrollment of the child through at least age 4, 6, or 8 years was required; fewer subjects were available at later follow-up ages due to attrition from the health maintenance

organization and administrative censoring (if the child did not reach age by end of 2014). Other

details pertaining to the study population have been reported elsewhere.[21]

Measures

Exposure: Prepregnancy BMI

Height and weight measurements were obtained from the mother's EMR data to

calculate prepregnancy BMI. The height measurement taken closest to the last menstrual

period (LMP) date was used as the prepregnancy height. The weight measurement taken

closest to the LMP date (within 6 months prior to 10 weeks after), was used as the

prepregnancy weight. Prepregnancy BMI was determined using CDC classification

categories: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5 – 24.9 kg/m^2),

overweight (BMI 25.0 – 29.9 kg/m^2), obese (BMI ≥30 kg/m^2).[22] Implausible

prepregnancy BMI values (BMI <12 kg/m^2 and BMI >81 kg/m^2) were set to missing. For

some analyses prepregnancy BMI was dichotomized into a series of indicator variables:

underweight vs normal, overweight vs normal, and obese vs normal.

Outcome: Childhood asthma

Childhood asthma was determined using a combination of ICD 9/10 codes and

asthma-related prescription medication dispensings. For a child to meet the asthma

outcome definition two criteria were required: (1) an inpatient discharge diagnosis code

for asthma (with the primary code for asthma or the primary code for acute respiratory

infection and the secondary code for asthma) or two outpatient asthma ICD 9/10 codes

(ICD-9 493 or ICD-10 J45) at least thirty days apart and (2) two controller prescription

medication dispenses at least thirty days apart, with at least one within twelve months of

the relevant follow-up age (4, 6, or 8 years). This allowed a child's asthma status to potentially change between follow-up ages.

Mediators: Child's BMI, GWG, and GA

Variables considered for mediation analyses were determined based on change in estimate analyses published previously.[21] These include child's BMI, GWG, and GA. Height and weight measurements were obtained from the child's EMR data. For each follow-up age (4, 6, and 8 years) the height and weight measurement closest to the child's previous birthday (within 6 months – allowing for dynamic timing of child wellness visits) were used to calculated BMI-for-age percentiles based on the CDC growth charts.[23] Categories included: underweight [<5th], normal [5th-85th], overweight [85th-95th], and obese [>95th]. Implausible values were determined using modified z-scores that identified extreme values and were set to missing.[24] For some analyses child's BMI was dichotomized as overweight/obese vs underweight/normal (because overweight BMI is also associated with higher risk of childhood asthma, it was grouped with obese BMI[10]). GA was defined as the length of pregnancy in weeks starting from the LMP date to the delivery date. For some analyses GA was dichotomized as preterm birth (<37 weeks gestation) vs full-term birth (≥37 weeks gestation). Total GWG was defined as delivery weight minus prepregnancy weight. Based on Institutes of Medicine (IOM) guidelines for recommended weight gain per prepregnancy BMI category,[11] GWG was categorized as inadequate (<28 lbs. for underweight BMI, <25 lbs. for normal BMI, <15 lbs. for overweight BMI, and <11 lbs. for obese BMI), adequate (28-40 lbs. for underweight BMI, 25-35 lbs. for normal BMI, 15-25 lbs. for overweight BMI, and 11-20 lbs. for obese BMI), or excessive (>40 lbs. for underweight BMI, >35 lbs. for normal BMI, >25 lbs. for

overweight BMI, and >20 lbs. for obese BMI). For some analyses GWG was

dichotomized as excessive vs inadequate/adequate or inadequate vs adequate/excessive.

Covariates

Other covariate information was collected from the EMR data in the KPNC

system to adjust for confounding. Maternal characteristics included age (<25, 25-29, 30-

34, 35-39, ≥40 years), education (<12, 12-15, ≥16 years), self-identified race and

ethnicity (White, Black, Asian/Pacific Islander, Hispanic, other/missing), asthma

(categorized as active during this pregnancy, past, or none; status determined using

prescription medication dispensing and diagnoses stated on medical intake forms),

allergies (yes/no; including diagnoses at any time for allergic rhinitis, atopic dermatitis,

food allergies, or other allergies), smoking during this pregnancy (yes/no). Child

characteristics were birth year (2005-2014), infant sex (male/female), and parity (first

born, second born, or third born or more).

Statistical Analysis

Causal mediation analyses is a useful approach to investigate the underlying

pathways of an observed association between an exposure (prepregnancy BMI) and an

outcome (childhood asthma), potentially through a mediating variable (child's BMI,

GWG, or GA).[20] For our study, the directed acyclic graph (DAG) in Figure 1

demonstrates the components of this mediation analysis, using child's BMI as an

example mediator (though GWG or GA can be substituted). The effect of prepregnancy

BMI on childhood asthma (arrow pointing from prepregnancy BMI to childhood asthma)

is the direct effect, while the path from prepregnancy BMI to child's BMI (or other

mediator) then to childhood asthma is the indirect effect. Complete mediation is detected

if prepregnancy BMI affects childhood asthma only through the mediating variable; otherwise, partial mediation is observed.[20]

In order to apply a causal interpretation to these mediation analyses, four assumptions are required, essentially the same assumptions required by traditional mediation analyses: no unmeasured confounding.[20] First, no unmeasured confounding of the relationship between prepregnancy BMI (exposure) and childhood asthma (outcome; C1 in Figure 1). Second, no unmeasured confounding of the relationship between the potential mediator and childhood asthma (C2 in Figure 1). Third, no unmeasured confounding of the relationship between prepregnancy BMI and the potential mediator (C3 in Figure 1). And fourth, no unmeasured confounding of the relationship between the potential mediator and childhood asthma caused by prepregnancy BMI (C4 in Figure 1). These confounding variables (C1-C4) can be included as an overall set of confounders during adjusted analyses (e.g., those listed above).

Causal inference test

Before implementing causal mediation models, we first identify potential mediating effects of child's BMI, GWG, and/or GA on the association between prepregnancy BMI and childhood asthma, using CIT.[19] The CIT evaluates four conditions assessing the relationships between the exposure (prepregnancy BMI), the mediator (child's BMI, GWG, or GA), and the outcome (childhood asthma): (1) prepregnancy BMI is associated with childhood asthma, (2) prepregnancy BMI is associated with the potential mediator, conditional on childhood asthma, (3) the potential mediator is associated with childhood asthma, conditional on prepregnancy BMI, and (4) prepregnancy BMI is independent of childhood asthma, conditional on the potential

mediator. If all four conditions are met, complete mediation is detected. However, partial mediation can be determined if the first three conditions are met, and the fourth condition shows an attenuated effect (closer to the null).[19]

Modified Poisson regression models with robust variance estimation[25,26] were used to estimate risk ratios (RR) and 95% confidence intervals (95% CI) for the four conditions for each potential mediator (child's BMI, GWG, and GA). All analyses were adjusted for *a priori* confounders[18,27,28] including maternal characteristics: age, education, race/ethnicity, asthma, allergies, and smoking; and child characteristics: birth year, parity, and infant sex. Analyses were repeated for each follow-up age (age 4, 6, and 8 years).

Causal Mediator Analyses

To estimate the extent to which the effect of prepregnancy BMI on childhood asthma is mediated through intermediate variables identified using CIT (child's BMI, GWG and/or GA), causal mediator models were applied.[20] This form of mediation analysis allows for the decomposition of the total effect into the natural (and controlled) direct and indirect effects, even in models with exposure-mediator interactions and non-linearities. This method uses logistic regression models for the binary outcome and binary mediator to estimate these effects as odds ratios (ORs; 95% CI are calculated using the delta method); or linear regression models for continuous outcome or mediator.

For example: we let Y indicate the binary outcome childhood asthma (1=yes, 0=no), A indicate the binary exposure prepregnancy BMI (e.g., 1=obese, 0=normal), M indicate the binary mediator (e.g., child's BMI 1=overweight/obese, 0=underweight/normal), and C indicate a set of additional covariates (e.g., those listed above). The outcome model and mediator model are given in Table 1.[20] If these models

are correctly specified and the no unmeasured confounding assumptions described above are met, then the natural direct effect (NDE) and the natural indirect effect (NIE) can be computed as ORs using the coefficients from the outcome and mediator models inputted into the equations shown in Table 1. The total effect is the product of these ORs (NDE*NIE).[20] Though these equations allow for exposure-mediator interaction, no statistical evidence for such interaction was observed in this study. In this case, the controlled direct effect is equal to the NDE. Also in the absence of exposure-mediator interaction the ORs for NDE and NIE reduce to be equivalent to traditional mediation analysis methods of estimating direct and indirect effects.[20,29] Example interpretations of these effects are also included in Table 1 using exposure categories of obese prepregnancy BMI vs normal and mediator categories of childhood overweight/obese BMI vs underweight/normal. Other exposure contrasts and potential mediators can be substituted in these interpretation examples.

These causal mediation analyses were implemented using macros developed by Valeri and VanderWeele (2013).[20] These macros could accommodate our binary outcome variable (childhood asthma) and binary or continuous mediator variables, and required binary exposure variables. As such, prepregnancy BMI was used as a series of indicator variables described above. Additionally, any categorical covariates (i.e., those listed above) needed to be included as series of indicator variables. These causal mediation analyses were performed for potential mediators that met the CIT conditions (1-4). Sensitivity analyses were performed operationalizing the mediator(s) as a continuous variable instead of binary. Additionally, low birth weight (<2500 grams vs ≥2500 grams) was considered as a mediator as an alternative to GA (preterm vs full-term). Analyses

were repeated for each follow-up cohort (age 4, 6, and 8 years) and were adjusted for *a priori* confounders. Additionally, as multiple mediators may be of interest in this setting, causal multiple mediator models were implemented with SAS code from VanderWeele and Vansteelandt (2014).[30]

Study protocols were approved by the University of Nevada, Reno and KPNC Institutional Review Boards (IRB). Consent to using EMR data for medical research was provided by all KPNC members upon enrollment. The reporting guidelines checklist for observational research using routinely collected data (RECORD)[31] was complete for this study.[21] All analyses were performed as complete case analyses and were completed in SAS 9.4 (SAS Institute, Cary, NC).

Results

In the age 4, 6, and 8 analyses, 95,723, 59,230 and 25,261 children were included in the complete case analyses respectively. Among them 5.3%, 7.8%, and 9.4%, respectively, met the outcome asthma definition (Table 2). Across cohorts, 2% of mothers had an underweight prepregnancy BMI, 45% had a normal prepregnancy BMI, 28% had an overweight prepregnancy BMI, and 26% had an obese class 1, 2, or 3 prepregnancy BMI (Table 3). Tables 2 and 3 show the strongest predictors of childhood asthma among child characteristics were infant sex (male), and child's obesity (BMI > 95th percentile); and among maternal characteristics were prepregnancy obesity, race (Black), active asthma, and allergies.

Causal Inference Test

The results of the CIT for all mediators are shown in Table 4. Binary child's BMI (overweight/obese vs underweight/normal) met the first three conditions and partly met

the fourth condition for all follow-up ages (4, 6, and 8 years). Prepregnancy BMI

(continuous) was associated with childhood asthma showing a 6%-7% increase in risk of

childhood asthma for each 5 unit (kg/m^2) increase in prepregnancy BMI, after controlling

for other covariates (condition 1). After additional control for child's BMI this

association was slightly reduced (condition 4). Prepregnancy BMI was associated with

child's BMI, after controlling for other covariates (condition 2). And child's BMI was

associated with childhood asthma, after controlling for other covariates and prepregnancy

BMI (condition 3). Together, this indicates that child's BMI partly mediates the

association between prepregnancy BMI and childhood asthma for all follow-up ages.

Similarly, binary GA (preterm vs full-term) met the first three conditions and partly met

fourth condition (Table 4) – also indicating that GA partly mediates the association

between prepregnancy BMI and childhood asthma for all follow-up ages. Excessive

GWG (excessive vs inadequate/adequate or inadequate vs excessive/adequate), however,

did not show mediating effects on the association between prepregnancy BMI and

childhood asthma for any follow-up ages. While excessive GWG met the first two

conditions, it was not associated with childhood asthma after controlling for

prepregnancy BMI (Table 4).

Causal Mediator Analyses

  The causal mediator models estimate the extent to which the potential mediators

that met the CIT conditions (child's BMI and GA) mediate the association between

prepregnancy BMI and childhood asthma. Figure 2 shows the results from these analyses

using binary mediators. Total effects showed increased odds of childhood asthma among

children born to mothers with overweight prepregnancy BMI (Age 4 $OR^{TE} = 1.09$, 95%

CI: 1.01, 1.17; Age 6 OR^{TE} = 1.11, 95% CI: 1.03, 1.20; Age 8 OR^{TE} = 1.06, 95% CI:

0.95, 1.18) and obese prepregnancy BMI (Age 4 OR^{TE} = 1.17, 95% CI: 1.08, 1.26; Age 6

OR^{TE} = 1.24, 95% CI: 1.14, 1.34; Age 8 OR^{TE} = 1.19, 95% CI: 1.06, 1.33) compared to

children born to mothers with normal prepregnancy BMI.

Focusing on child's BMI (overweight/obese vs underweight/normal) as the

potential mediator, the obese prepregnancy BMI NIE indicates the odds of childhood

asthma among children born to mothers with obese prepregnancy BMI were elevated

because of their current level of childhood BMI rather than at the level equal to children

born to mothers with normal prepregnancy BMI (Age 4 OR^{NIE} = 1.03, 95% CI: 1.01,

1.04; Age 6 OR^{NIE} = 1.06, 95% CI: 1.04, 1.08; Age 8 OR^{NIE} = 1.07, 95% CI: 1.03, 1.10).

The NDE indicates that even if children born to mothers with obese prepregnancy BMI

and children born to mothers with normal prepregnancy BMI had the same levels of

childhood BMI (i.e., all children had underweight/normal BMI), children born to mothers

with obese prepregnancy BMI would still have 1.11-1.17 times the odds of childhood

asthma compared to children born to mothers with normal prepregnancy BMI (Age 4

OR^{NDE} = 1.14, 95% CI: 1.05, 1.23; Age 6 OR^{NDE} = 1.17, 95% CI: 1.07, 1.27; Age 8

OR^{NDE} = 1.11, 95% CI: 0.98, 1.25). Similar patterns are shown for the underweight vs.

normal NDE and NIE and for overweight vs. normal NDE and NIE, though they were not

as strong. These demonstrate that the effect of prepregnancy BMI on childhood asthma

was, in a small part, partially explained by the child's own BMI. A sensitivity analysis

using child's BMI as a continuous mediator provided the same conclusions (Figure 3).

Focusing on GA (preterm vs full-term) as the potential mediator, there was no

evidence that the effect of prepregnancy BMI on childhood asthma was meaningfully

mediated through GA. The NIE reported for each prepregnancy BMI category (compared to normal prepregnancy BMI) were predominately null and did not substantially contribute to the total effects shown (Figure 3); whereas the NDE were nearly identical to the total effects reported. These patterns were confirmed in sensitivity analyses using continuous GA as the potential mediator (Figure 3). Additionally, as an alternative to GA, low birth weight (<2500 grams vs ≥2500 grams) was also considered as a mediator, though it showed no evidence of mediation either (not shown).

In this setting, since multiple mediators were of interest (child's BMI and GA), multiple mediator analyses were performed.[30] Similar results for child's BMI were observed, however, when GA was considered as an additional mediator, there was no change to the natural direct and indirect effects. This indicates that there is no effect of prepregnancy BMI on childhood asthma through GA, but not through child's BMI.

Discussion

This study, including over 95,000 mother-child pairs across multiple follow-up ages, evaluated the potential mediating effect childhood BMI, GWG, and/or GA on the association between prepregnancy BMI and childhood asthma. GWG did not meet the CIT conditions to be identified as a mediator as excessive or inadequate GWG was not associated with childhood asthma. Child's BMI and GA did meet the CIT conditions and were included in causal mediation analyses (as both binary and continuous variables). Child's BMI did appear to partially mediate the effect of prepregnancy BMI on childhood asthma, but there was weak evidence to conclude the same about GA.

There are limited studies that have investigated mediating pathways between prepregnancy BMI and childhood asthma; only a few of them have addressed the

potential mediating effects of child's BMI or GA, and none, to our knowledge, have investigated GWG as a mediator. We selected these three factors to evaluate because they impacted our previously reported associations between prepregnancy BMI and childhood asthma and could plausibly be on the causal pathway.[21] Previous studies have presented inconsistent results regarding the potential mediating effect of childhood BMI. Among studies that compared models with and without childhood BMI, several observed no change in their estimates,[14–16] or only slightly attenuated effects.[12,13] Of these slightly attenuated effects, the largest differences between models with and without adjustment for childhood BMI were reported by Harpsøe et al. (2013), showing a 4%-7% decrease in adjusted ORs when childhood BMI was included in the models for prepregnancy BMI and childhood asthma.[13] This could indicate the association between prepregnancy BMI and childhood asthma may be mediated, at least partly, by childhood BMI, though independent effects of prepregnancy BMI on childhood asthma seem to remain. However, more formal mediation analyses, including CIT and regression based single mediator models that looked beyond attenuated effects, found weak to no evidence of mediation by child's BMI.[17,18]

GWG and GA have been less of a focus in previously published analyses regarding potential mediation pathways between prepregnancy BMI and childhood asthma. Only two studies have included GA as a potential mediator, both found no change in their estimates when GA was included in their models.[13,16] And, currently, there are no previous studies that have identified or evaluated GWG as a potential mediator in the prepregnancy BMI-childhood asthma association.

There is strong evidence linking maternal obesity to childhood overweight/obesity, with a recent meta-analysis reporting a 264% increase in the odds of childhood obesity among children born to mothers who were obese.[7] While a consensus exists that childhood overweight/obesity has many dynamic causes (including physiological, environmental, social and behavioral) there is also some evidence that in-utero epigenetic processes that affect DNA and the gut microbiome could contribute to childhood overweight/obesity.[32] A consistent link between childhood asthma and childhood overweight/obesity is evident in the literature, though some studies have difficulty establishing which condition came first. Several recent studies have evaluated longitudinal data and found that increasing BMI among children increased the risk of developing incident asthma.[8,33,34] The main mechanisms thought to influence this relationship are similar to those for adults: inflammation and reduced lung function related to obesity.[35]

This study included at least 95,723 mother-child pairs for complete case analysis, making it the largest study to date in the US on this topic. Using EMR data, instead of self-reported data, this study included several covariates, related to both the mother and the child, that previous work did not have available. Additionally, the EMR data included prospectively collected serial anthropometric measurements for mothers and children, as well as routinely collected objective medication dispensings and diagnostic data. Child's asthma outcome status was determined using a combination of ICD 9/10 codes and prescription medication dispensings and was assessed at multiple follow-up ages, including after age 5 when asthma diagnosis are known to be more reliable.[36] Using causal mediation models has advantages over traditional mediation methods in that they

can account for exposure-mediator interaction and in some cases mediator-mediator interaction.[20,30] Though there was no statistical evidence of exposure-mediator interaction in this analysis, causal mediation methods are still preferrable because they also allow for effect decomposition in the form of ORs, and although the assumptions for causal mediation are the same as traditional mediation, they are stated more formally.[20]

All causal interpretations are being made under the four assumptions of no unmeasured confounding (described previously). It is possible that there is residual confounding in the exposure-outcome (C1 in Figure 1) or mediator-outcome (C2 in Figure 1) relationships, which could violate these assumptions. This could be due to unmeasured or poorly measured factors such as genetics, socioeconomic status, lifestyle factors, or environment.

Using weight measurements up to 10 weeks into pregnancy for prepregnancy BMI calculations (for some women) may have led to exposure misclassification (in that some women may have already gained weight). However, weight gain in the first weeks of pregnancy is typically between 1 and 4 lbs.[11] Another limitation could be that the utilization of EMR data and algorithms to determine child's asthma outcome status may have led to outcome misclassification, which would affect both the NDE and NIE estimates. While the comprehensive medication and diagnoses histories available is a strength of this study, the study population represents fully insured mother-child pairs that may not be generalizable to other populations. Finally, selection bias may occur from mother-child pairs being excluded due to conducting a complete case analysis. Though, missing data was not related to any other study variables except birth year (indicating increases in the use of EMR over time).[21]

In conclusion, after evaluating three potential mediation factors on the relationship between prepregnancy BMI and childhood asthma, GWG was not identified as a mediator, GA indicated little to no evidence of mediation, and child's overweight/obesity showed a modest mediating effect. Using causal mediation techniques, we conclude that the association between prepregnancy BMI and childhood asthma is at least partly mediated by childhood overweight/obesity, although, most of the effect of prepregnancy BMI on childhood asthma appears to be independent of childhood overweight/obesity. Since the prevalence of prepregnancy obesity, childhood obesity, and childhood asthma continue to increase it will be important for future research to further examine the causal pathways linking these conditions. This could further elucidate the underlying biological mechanisms between these diseases and build evidence for potential interventions.

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Figure 3.1: Directed acyclic graph of prepregnancy BMI and child's asthma showing

mediating pathways and confounding
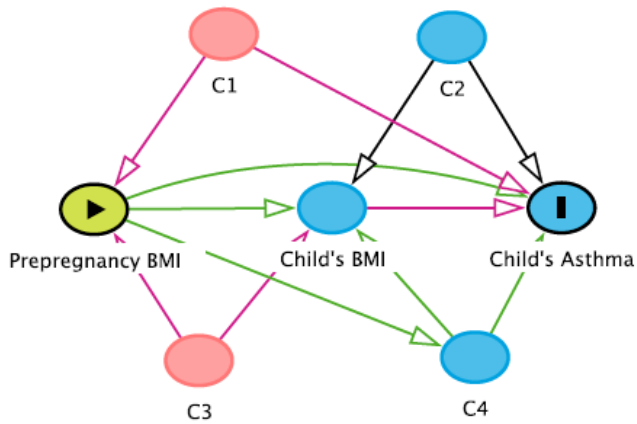
Abbreviations: BMI – body mass index
Legend:
Exposure = prepregnancy BMI
Outcome = child's asthma
Mediator = child's BMI
Green arrow = causal pathway
Pink arrow = biasing pathway
Notes: C1 denotes an exposure-outcome confounder, C2 denotes a mediator-outcome confounder, C3 denotes an exposure-mediator confounder, and C4 denotes a mediator-outcome confounder caused by the exposure. Adequate control for these confounders is necessary to apply causal interpretation to these mediation analyses (i.e., meeting the no unmeasured confounding assumptions). Child's BMI is used as an example mediator in this figure – it can be substituted for the other mediators of interest: gestational weight gain and gestational age.

Table 3.1: Equations for models and odds ratio natural direct and indirect effects for binary outcome and binary mediator in causal

mediation analyses

Description	Equation[a]
<u>Outcome model</u>: logistic regression model for childhood asthma (Y), including prepregnancy BMI as the exposure (A), binary mediator (M), and set of potential confounders (C)	$Logit\{P(Y = 1|a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$
<u>Mediator model</u>: logistic regression model for binary mediator (M) including prepregnancy BMI as the exposure (A), and set of potential confounders (C)	$Logit\{P(M = 1|a, c)\} = \beta_0 + \beta_1 a + \beta_2' c$
<u>Natural direct effect</u>: change in odds of the outcome for varying exposure level, while holding the mediator fixed at the value it would have taken under no exposure For example[b]: The change in odds of childhood asthma (outcome) for children born to mothers with obese prepregnancy BMI (exposed) compared to normal prepregnancy BMI (unexposed), if the average childhood BMI (mediator) among children born to mothers with normal prepregnancy BMI (unexposed) were applied to everyone	$OR^{NDE} = \dfrac{exp(\theta_1 a)\{1 + exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2' c)\}}{exp(\theta_1 a^*)\{1 + exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta_2' c)\}}$ With no exposure-mediator interaction (θ_3=0) reduces to[c]: $OR^{NDE} = exp\ (\theta_1\{a - a^*\})$
<u>Natural indirect effect</u>: change in odds of the outcome for varying the mediator level (from what it would be under exposure to what it would be under no exposure), while holding the exposure fixed For example[b]: The change in odds of childhood asthma (outcome) among children born to mothers with obese prepregnancy BMI (exposed) for their observed childhood BMI (mediator) compared to if their childhood BMI (mediator) were equal to that of children born to mothers with normal prepregnancy BMI (unexposed)	$OR^{NIE} = \dfrac{\{1 + exp(\beta_0 + \beta_1 a^* + \beta_2' c)\}\{1 + exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2' c)\}}{\{1 + exp(\beta_0 + \beta_1 a + \beta_2' c)\}\{1 + exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2' c)\}}$ With no exposure-mediator interaction (θ_3=0) reduces to[c]: $OR^{NIE} = exp\ (\theta_2 \beta_1\{a - a^*\})$

Abbreviations: BMI – body mass index

[a] In the odds ratio equations, 'a' represents the exposure level set to 1 (underweight, overweight, or obese maternal prepregnancy BMI), and 'a*' represents the exposure level set to 0 (normal maternal prepregnancy BMI).

[b] Examples can be adapted for interpretation of other exposure contrasts (i.e., underweight vs normal and overweight vs normal) and each potential mediator of interest (i.e., gestational weight gain and gestational age)

[c] There was no evidence of statistical exposure-mediator interactions in this study, therefore the natural direct effect is equivalent to the controlled direct effect. Additionally, in the absence of exposure-mediator interactions, these equations can be reduced

Table 3.2: Child characteristics for follow-up ages 4, 6, & 8

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	5070 (5.3)	95723	4616 (7.8)	59230	2370 (9.4)	25261
Child BMI[a] (pct)						
Underweight (<5th)	241 (5.2)	4632	214 (8.1)	2650	116 (10.6)	1095
Normal (5th-84th)	3379 (4.9)	68361	2993 (7.6)	39280	1492 (9.0)	16500
Overweight (85th-95th)	816 (5.9)	13820	697 (8.7)	8015	364 (10.5)	3471
Obese (>95th)	634 (7.1)	8910	599 (11.4)	5270	308 (13.0)	2363
Mean [SD][b]	16.6 [1.7]	16.3 [1.6]	16.5 [2.3]	16.1 [1.9]	17.2 [3.1]	16.7 [2.7]
Gestational Age (weeks)						
<37 (preterm)	570 (9.5)	5993	481 (12.8)	3753	235 (14.3)	1641
≥37 (full-term)	4500 (5.0)	89730	4135 (7.5)	55477	2135 (9.0)	23620
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]
Infant Sex						
Male	3243 (6.6)	48942	2916 (9.6)	30278	1478 (11.4)	13004
Female	1827 (3.9)	46781	1700 (5.9)	28952	892 (7.3)	12257
Parity						
First Born	2109 (5.0)	42381	1949 (7.6)	25664	1005 (9.2)	10967
Second Born	1953 (5.6)	34872	1749 (8.1)	21627	887 (9.6)	9222
Third Born +	1008 (5.5)	18470	918 (7.7)	11939	478 (9.4)	5072

Abbreviations: BMI – body mass index

[a]Child BMI percentiles calculated using height and weight measurements

Actual BMI measured at age 3, 5, or 7 respectively

Note: based on complete case analysis

Table 3.3: Maternal characteristics for follow-up ages 4, 6, & 8

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	5070 (5.3)	95723	4616 (7.8)	59230	2370 (9.4)	25261
Prepregnancy BMI (kg/m^2)[a]						
Underweight	102 (4.4)	2334	94 (6.6)	1422	52 (8.1)	639
Normal	2261 (4.7)	47632	2029 (6.9)	29556	1063 (8.5)	12548
Overweight	1426 (5.5)	25838	1296 (8.2)	15858	650 (9.7)	6727
Obese 1, 2, & 3	1281 (6.4)	19919	1197 (9.7)	12394	605 (11.3)	5347
Mean [SD]	27.0 [6.3]	261 [5.9]	27.0 [6.3]	26.1 [5.9]	26.9 [6.4]	26.1 [5.9]
Total GWG[b]						
Inadequate	1086 (5.5)	19657	902 (7.6)	11866	458 (9.2)	4964
Adequate	1579 (5.1)	31266	1454 (7.4)	19523	740 (9.0)	8244
Excessive	2405 (5.4)	44800	2260 (8.1)	27841	1172 (9.7)	12053
Mean [SD]	29.1 [14.2]	29.8 [13.6]	29.4 [13.9]	29.9 [13.6]	29.9 [14.4]	30.1 [13.8]
Age (years)						
<25	520 (6.3)	8195	484 (9.4)	5146	264 (11.5)	2304
25-29	1320 (5.1)	25802	1186 (7.3)	16264	634 (9.1)	6962
30-34	1930 (5.3)	36137	1671 (7.6)	21930	816 (8.9)	9168
35-39	1039 (5.0)	20604	1018 (8.0)	12718	522 (9.5)	5502
≥40	261 (5.2)	4985	257 (8.1)	3172	134 (10.1)	1325
Education (years)						
<12	194 (5.8)	3354	201 (9.1)	2208	112 (11.0)	1014
12-15	2312 (5.9)	39260	2216 (8.8)	25128	1179 (10.6)	11136
16+	2564 (4.8)	53109	2199 (6.9)	31894	1079 (8.2)	13111
Race/Ethnicity						
White	1809 (4.4)	41490	1597 (6.2)	25662	807 (7.4)	10963
Black	474 (8.8)	5365	402 (12.1)	3330	225 (15.0)	1503
API	1453 (5.4)	27066	1368 (8.2)	16599	673 (9.8)	6850
Hispanic	1295 (6.1)	21192	1224 (9.2)	13308	661 (11.3)	5834
Other	39 (6.4)	610	25 (7.6)	331	4 (3.6)	111
Asthma[c]						
Active	1140 (9.3)	12295	1045 (14.4)	7281	500 (16.5)	3032
Past	445 (7.0)	6319	423 (10.6)	3999	230 (12.2)	1878
None	3485 (4.5)	77109	3148 (6.6)	47950	1640 (8.1)	20351
Allergies[d]						
Yes	3078 (6.4)	48460	2929 (9.4)	31102	1551 (11.1)	13961
No	1992 (4.2)	47263	1687 (6.0)	28128	819 (7.2)	11300
Smoking During Pregnancy						

Yes	506 (5.8)	8697	415 (8.2)	5037	202 (9.9)	2047
No	4564 (5.2)	87026	4201 (7.8)	54193	2168 (9.3)	23214

Abbreviations: BMI – body mass index, GWG – gestational weight gain

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1, 2, & 3 (≥30 kg/m^2)

[b]Calculated as delivery weight minus prepregnancy weight; based on Institutes of Medicine recommend weight gain per prepregnancy BMI category: adequate GWG range for underweight BMI = 28-40 lbs., normal BMI = 25-35 lbs., overweight BMI = 15-25 lbs., and obese BMI = 11-20 lbs.

[c]Asthma during this pregnancy determined using diagnoses reported on medical intake forms and medication dispensing

[d]Maternal allergies including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the electronic medical record

Note: based on complete case analysis

Table 3.4: Causal inference test (CIT) of potential mediators in the association between prepregnancy BMI and childhood asthma

Condition	Child's BMI[d]			Gestational Age[e]			Excessive GWG[f]		
Age 4 (n = 95,723)	RR	95% CI	Condition Met	RR	95% CI	Condition Met	RR	95% CI	Condition Met
(1) Prepregnancy BMI[a] is associated with childhood asthma	1.07	(1.04, 1.09)	Yes	1.07	(1.04, 1.09)	Yes	1.07	(1.04, 1.09)	Yes
(2) Prepregnancy BMI[a] is associated with mediator, after controlling for childhood asthma	1.23	(1.22, 1.24)	Yes	1.11	(1.09, 1.13)	Yes	1.09	(1.08, 1.09)	Yes
(3) Mediator[b] is associated with childhood asthma, after controlling for prepregnancy BMI[c]	1.20	(1.13, 1.28)	Yes	1.71	(1.58, 1.86)	Yes	0.98	(0.93, 1.04)	No
(4) Prepregnancy BMI[a] is independent of childhood asthma, after controlling for mediator	1.05	(1.03, 1.08)	Partial	1.06	(1.04, 1.08)	Partial	1.07	(1.04, 1.09)	No
Age 6 (n = 59,230)									
(1) Prepregnancy BMI[a] is associated with childhood asthma	1.07	(1.04, 1.09)	Yes	1.07	(1.04, 1.09)	Yes	1.07	(1.04, 1.09)	Yes
(2) Prepregnancy BMI[a] is associated with mediator, after controlling for childhood asthma	1.28	(1.27, 1.29)	Yes	1.11	(1.08, 1.14)	Yes	1.09	(1.08, 1.09)	Yes
(3) Mediator[b] is associated with childhood asthma, after controlling for prepregnancy BMI[c]	1.25	(1.18, 1.33)	Yes	1.55	(1.42, 1.69)	Yes	1.05	(0.99, 1.11)	No
(4) Prepregnancy BMI[a] is independent of childhood asthma, after controlling for mediator	1.05	(1.02, 1.07)	Partial	1.06	(1.04, 1.08)	Partial	1.06	(1.04, 1.09)	Partial
Age 8 (n = 25,261)									
(1) Prepregnancy BMI[a] is associated with childhood asthma	1.06	(1.02, 1.09)	Yes	1.06	(1.02, 1.09)	Yes	1.06	(1.02, 1.09)	Yes
(2) Prepregnancy BMI[a] is associated with mediator, after controlling for childhood asthma	1.32	(1.30, 1.34)	Yes	1.07	(1.03, 1.12)	Yes	1.09	(1.08, 1.10)	Yes
(3) Mediator[b] is associated with childhood asthma, after controlling for prepregnancy BMI[c]	1.24	(1.14, 1.35)	Yes	1.45	(1.28, 1.64)	Yes	1.04	(0.96, 1.13)	No
(4) Prepregnancy BMI[a] is independent of childhood asthma, after controlling for mediator	1.03	(1.00, 1.07)	Partial	1.05	(1.02, 1.09)	Partial	1.05	(1.02, 1.09)	Partial

Abbreviations: BMI – body mass index, RR – risk ratio, GWG – gestational weight gain
[a] Per 5 unit (kg/m^2) increase in prepregnancy BMI

[b] Binary mediator definitions

[c] Continuous prepregnancy BMI

[d] Based on BMI-for-age percentiles; coded as overweight[85th-95th]/obese[>95th] = 1, and underweight[<5th]/normal[5th-85th] = 0

[e] Coded as preterm (<37 weeks gestation) = 1, and full-term (≥37 weeks gestation) = 0

[f] Based on Institutes of Medicine recommended weight gain per prepregnancy BMI category: adequate GWG for underweight BMI = 28-40 lbs., adequate GWG for normal BMI = 25-35 lbs., adequate GWG for overweight BMI = 15-25 lbs., adequate GWG for obese BMI = 11-20 lbs.; coded as excessive GWG = 1, and inadequate/adequate GWG = 0. Comparing inadequate to adequate/excessive yielded the same conclusions.

All models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, and infant sex.

Figure 3.2: Natural direct, indirect, and total effects of prepregnancy BMI on child's asthma with binary mediators
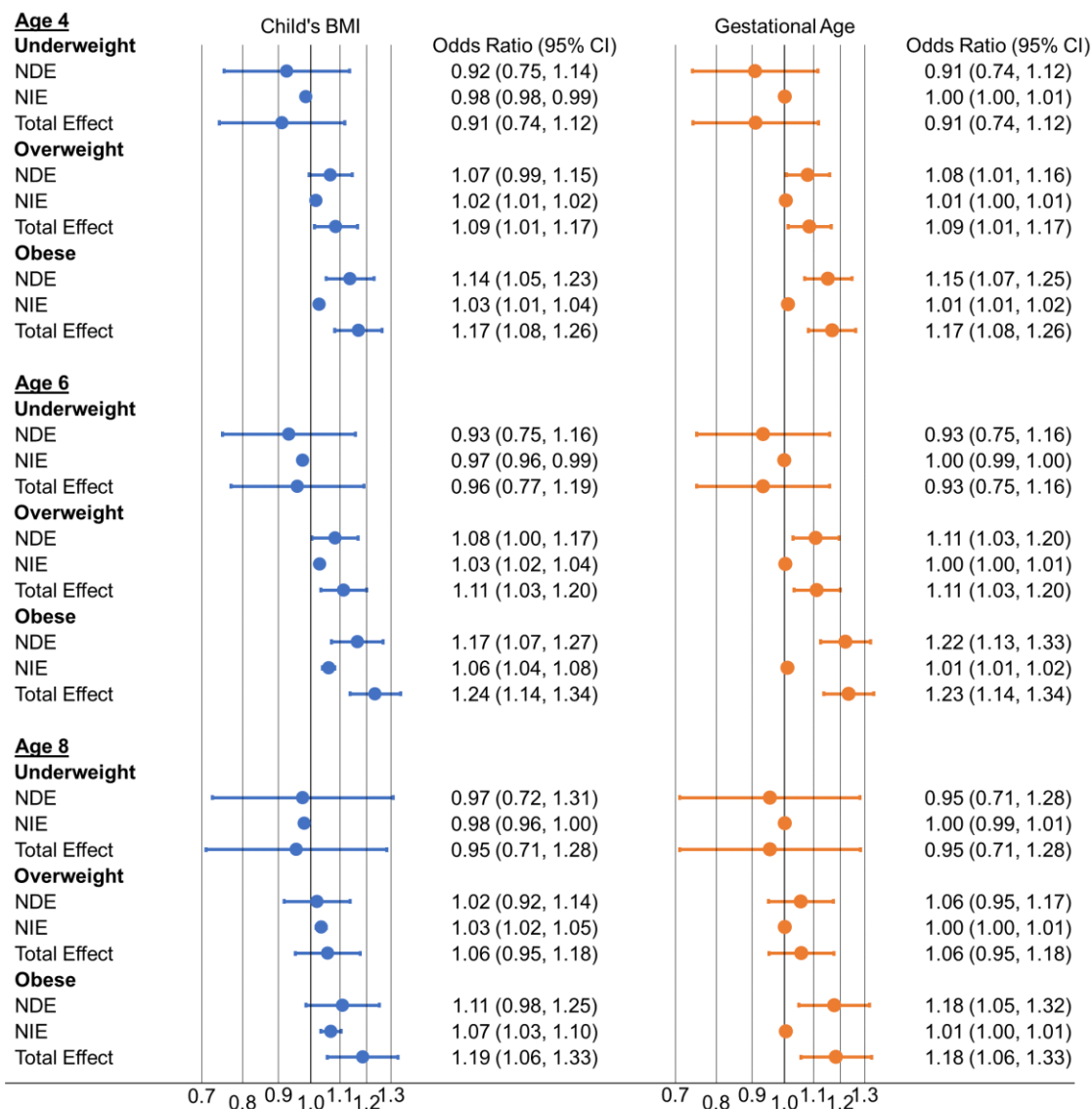
Abbreviations: BMI – body mass index, NDE – natural direct effect, NIE – natural indirect effect

Notes: Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal ($18.5 – 24.9$ kg/m^2; reference), overweight ($25.0 – 29.9$ kg/m^2), obese (≥30 kg/m^2). Child's BMI based on BMI-for-age percentiles; coded as overweight[85th-95th]/obese[>95th] = 1, and underweight[<5th]/normal[5th-85th] = 0. Gestational age coded as preterm (<37 weeks gestation) = 1, and full-term (≥37 weeks gestation) = 0.

Figure 3.3: Direct, indirect, and total effects of prepregnancy BMI on child's asthma with continuous mediators

Age 4	Child's BMI Odds Ratio (95% CI)	Gestational Age Odds Ratio (95% CI)
Underweight		
NDE	0.93 (0.76, 1.14)	0.90 (0.73, 1.11)
NIE	0.98 (0.96, 0.99)	1.01 (1.00, 1.02)
Total Effect	0.91 (0.74, 1.12)	0.91 (0.74, 1.12)
Overweight		
NDE	1.07 (0.99, 1.14)	1.08 (1.01, 1.16)
NIE	1.02 (1.01, 1.03)	1.00 (1.00, 1.01)
Total Effect	1.09 (1.01, 1.16)	1.08 (1.01, 1.16)
Obese		
NDE	1.13 (1.05, 1.23)	1.15 (1.06, 1.24)
NIE	1.03 (1.02, 1.04)	1.01 (1.01, 1.02)
Total Effect	1.17 (1.08, 1.26)	1.16 (1.08, 1.26)
Age 6		
Underweight		
NDE	0.97 (0.78, 1.20)	0.93 (0.75, 1.15)
NIE	0.96 (0.94, 0.98)	1.01 (1.00, 1.01)
Total Effect	0.93 (0.75, 1.16)	0.93 (0.75, 1.16)
Overweight		
NDE	1.08 (1.00, 1.16)	1.11 (1.03, 1.20)
NIE	1.03 (1.02, 1.04)	1.00 (1.00, 1.00)
Total Effect	1.11 (1.03, 1.20)	1.11 (1.03, 1.20)
Obese		
NDE	1.16 (1.07, 1.27)	1.22 (1.12, 1.32)
NIE	1.06 (1.04, 1.08)	1.01 (1.01, 1.02)
Total Effect	1.24 (1.14, 1.34)	1.23 (1.13, 1.34)
Age 8		
Underweight		
NDE	1.00 (0.74, 1.34)	0.95 (0.70, 1.27)
NIE	0.95 (0.92, 0.98)	1.01 (1.00, 1.02)
Total Effect	0.95 (0.71, 1.28)	0.95 (0.71, 1.28)
Overweight		
NDE	1.02 (0.91, 1.13)	1.06 (0.95, 1.18)
NIE	1.04 (1.02, 1.06)	1.00 (0.99, 1.00)
Total Effect	1.06 (0.95, 1.18)	1.06 (0.95, 1.18)
Obese		
NDE	1.10 (0.98, 1.24)	1.17 (1.04, 1.32)
NIE	1.08 (1.04, 1.11)	1.01 (1.00, 1.01)
Total Effect	1.19 (1.06, 1.33)	1.18 (1.05, 1.33)

Abbreviations: BMI – body mass index, NDE – natural direct effect, NIE – natural indirect effect
Notes: Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2; reference), overweight (25.0 – 29.9 kg/m^2), obese ($\geq$30 kg/m^2). Child's BMI based on actual measured BMI (kg/m^2) at age 3, 5, and 7 respectively. Gestational age in weeks.

Chapter 4: Gestational Weight Gain and Childhood Asthma Risk

Abstract

Background: Prepregnancy obesity affects childhood asthma development, though the role of gestational weight gain (GWG) is uncertain. In this study, we investigate the association between GWG and childhood asthma risk.

Methods: Electronic medical records from mother-child pairs enrolled in Kaiser Permanente Northern California were used to follow a cohort of children from birth (in 2005-2014) until age 4 (n=93,389) and 6 (n=57,808). Childhood asthma was defined at each age using ICD codes and asthma-related medication dispensings. Several GWG (delivery weight minus prepregnancy weight) metrics were used including continuous and categorical total GWG, Institutes of Medicine categories (inadequate, adequate, excessive), trimester-specific total and rates of GWG (first trimester, second/third trimester). Analyses were stratified by prepregnancy BMI (normal [18.5-24.9], overweight [25-29.9], obese class 1 [30-34.9], and obese class 2/3 [≥35]). We also implemented the parametric g-formula to estimate the risk of childhood asthma, controlling for time-varying confounding.

Results: Most metrics of GWG, including those accounting for time-varying confounding, showed no association with childhood asthma risk; except for an increased risk for increasing first trimester GWG rate among mother-child pairs with normal or overweight prepregnancy BMI. The risk ratios (RR) and 95% confidence intervals (CI) per 1lb/week increase were: 1.12 (95%CI: 1.04, 1.21) and 1.14 (1.03, 1.23) for age 4 and 1.18 (1.09, 1.28) and 1.09 (1.01, 1.18) for age 6.

Conclusions: This large cohort study stratified by prepregnancy BMI, showed little evidence of an effect of GWG on childhood asthma risk, though a modest association was observed for first trimester GWG rate.

Introduction

Steady increases in the prevalence of childhood asthma,[1] maternal prepregnancy obesity,[2] and excessive gestational weight gain (GWG)[3] has brought attention to the relationships shared between these factors. There is a large body of evidence that suggests there is a positive association between maternal prepregnancy obesity and the development of asthma in childhood. Though, fewer studies have investigated the role of GWG in a child's risk of developing asthma. A recently updated meta-analysis found evidence for a U-shaped association between GWG and childhood asthma risk. Compared to normal GWG (10-15 kg), very high GWG (> 25 kg; adjusted odds ratio [OR]: 1.24, 95% confidence interval [CI]: 1.04, 1.47), moderately high GWG (20-25 kg; adjusted OR: 1.12, 95% CI:1.04, 1.21), and very low GWG (< 5 kg; adjusted OR: 1.26, 95% CI:1.08, 1.47) were associated with increased risk of childhood asthma.[4] Though, other individual study results have been inconsistent. Many find an association between high GWG and childhood asthma,[5–7] but only suggestive evidence of an association between low GWG and childhood asthma risk.[7,8] However, others find no association at all.[9,10]

The mechanisms linking GWG to childhood asthma are not clear. One possibility is similar to the potential mechanisms linking prepregnancy obesity and childhood asthma: inflammation. Pregnancy itself gives rise to proinflammatory conditions, especially in the first trimester, and is considered a natural inflammatory state.[11]

Inflammatory markers (such as high sensitivity C-reactive protein and serum amyloid A) can increase 18%-25% in women who gain excessive weight (according to Institutes of medicine [IOM] guidelines[12]) during pregnancy.[13] Changes in the fetal microbiome due to increases in circulating inflammatory markers can influence early immunological development and cause immune deficiencies associated with asthma development in childhood.[14]

It is important to consider the relationship between GWG and gestational duration. Both vary over time but commonly are treated as time-fixed variables such as total GWG (a summary measure expressing cumulative weight gained throughout pregnancy) and gestational age at delivery (a summary of indicator variables indicating whether a baby was born at a given week of gestation).[15] At any given week of gestation, the current GWG and gestational age can affect each other and influence their trajectory throughout pregnancy (known as time-varying confounding).[16] When the outcome of interest is associated with gestational age, like childhood asthma in this study, the relationship between GWG and gestational age must be accounted for to avoid biased estimates.[15,17] For example, longer pregnancies allow for more opportunity to gain weight; those who give birth cannot gain any more weight related to pregnancy. Preterm birth (gestational age <37 weeks) is a risk factor for childhood asthma; therefore, cumulative GWG is lower among those at high risk of childhood asthma (highlighting confounding). Additionally, if GWG causes a woman to give birth early, gestational age would be an intermediate variable between GWG and childhood asthma (adjusting for which can result in selection bias). This can result in an underestimation of the effect of GWG on childhood asthma. The directed acyclic graph (DAG) in Figure 1 (created using

DAGitty[18]) helps visualize this relationship. The parametric g-formula[16] can be used to estimate the causal effect of time-varying exposure (GWG) on an outcome of interest (childhood asthma) from longitudinal data while controlling for time-varying confounding (gestational age).

This study aims to further investigate the association between GWG and childhood asthma risk with attention to methodological issues in evaluating GWG in pregnancy that can result in bias.[17] We adjust for pregnancy duration (gestational age at birth) using different approaches and stratify analyses by prepregnancy BMI when evaluating the main effects of GWG on childhood asthma risk. Several different metrics of GWG are applied, including the use of multiple weight measurements throughout pregnancy, as well as the parametric g-formula to account for the time-varying nature of GWG and time-varying confounding by gestational age.

Methods

Study Population

We included singleton mother-child pairs who gave birth between 2005-2014 and were enrolled in Kaiser Permanente Northern California (KPNC) throughout pregnancy. Children were required to be continuously enrolled through at least age 4 or 6 years; fewer mother-child pairs were available at later follow-up ages due to administrative censoring (if the child did not reach age by end of 2014) and attrition from the health maintenance organization. Other details pertaining to the study population have been reported elsewhere.[19]

Measures

Exposure: Gestational Weight Gain

Total GWG was defined as delivery weight minus prepregnancy weight. Delivery weight was defined as the weight measurement on the visit date closest to the mother's hospital admission date (within 3 days prior), or, if not available, the weight measurement on the visit date closest to the mother's delivery date (within 7 days prior). The weight measurement on the visit date closest to the mother's last menstrual period (LMP) date, but not more than 6 months prior or 10 weeks after, was used for prepregnancy weight. This total GWG was then categorized in 10 lbs. increments (<10, 10-19, 20-29, 30-39, 40-49 and ≥50).

Additionally, total GWG was categorized according to the IOM recommended ranges for GWG at gestational age of delivery, which are defined separately for prepregnancy BMI categories.[12] Every woman's observed total GWG was compared to the expected adequate GWG at gestational ag of delivery. Expected adequate GWG at gestational age of delivery was calculated by the equation: recommended first trimester total weight gain + [(gestational age at weight measurement at or before delivery – 13 weeks) * recommended rate of gain in the second and third trimesters],[20] where the recommended first trimester total weight gain was 1.1–4.4 lbs. for every woman, and recommended second and third trimester weekly rate of weight gain was 1-1.3 lbs. per week for underweight BMI, 0.8-1 lb. per week for normal BMI, 0.5-0.7 lbs. per week for overweight BMI, and 0.4-0.6 lbs. per week for all obese BMI classes.[12] Women who's total GWG were below, within, or above these ranges were considered to have inadequate, adequate, or excessive weight gain, respectively.[12]

Total GWG in the first trimester was defined as the last weight measurement in the first trimester (between 10-13 weeks gestation, or if missing, between 14-16 weeks

gestation) minus prepregnancy weight. Total GWG in the second/third trimester was

defined as delivery weight minus the first weight measurement in the second trimester

(between 14-17 weeks, or if missing, between 12-13 weeks). If a woman did not have

weight measurements in these range of weeks, a trimester-specific total GWG (first or

second/third) was not calculated. Trimester-specific rates of weight gain were calculated

using the total weight gain for that trimester (first trimester and second/third trimester)

divided by the number of weeks between the first and last measurements in that trimester.

Outcome: Childhood asthma

Childhood asthma was defined using a combination of International Classification

of Disease (ICD) 9/10 diagnosis codes and asthma-related prescription medication

dispensings. Two criteria were required: (1) an inpatient discharge diagnosis code for

asthma (with the primary code for asthma, or the primary code for acute respiratory

infection and the secondary code for asthma) or two outpatient asthma ICD 9/10 codes

(ICD-9 493 or ICD-10 J45) at least thirty days apart, and (2) two controller prescription

medication dispenses at least thirty days apart, with at least one dispensing within twelve

months of the relevant follow-up age (age 4 or 6 years). This permitted a child's asthma

status to change between the age 4 and age 6 follow-up points. .

Covariates

Prepregnancy BMI was calculated using height and weight measurements

obtained from the mother's EMR data. The height measurement taken closest to the LMP

date was used as the prepregnancy height and prepregnancy weight was defined as

previously described. Prepregnancy BMI was categorized using CDC classifications:

underweight (BMI <18.5 kg/m^2), normal (BMI 18.5 – 24.9 kg/m^2), overweight (BMI

$25.0 - 29.9 \text{ kg/m}^2$), obese class 1 (BMI $30 - 34.9 \text{ kg/m}^2$), obese class 2 (BMI $35 - 39.9$

kg/m^2), and obese class 3 (BMI $40+ \text{ kg/m}^2$).[21] Obese class 2 and 3 were combined due to

small sample sizes in each category. Observations with implausible prepregnancy BMI

values (BMI <12 and BMI>81) were excluded. Gestational age was defined as the length

of pregnancy in weeks starting from the LMP date to the delivery date and categorized as

<32, 32, 33, 34, 35, 36, 37, 38, 39, 40, or ≥41 weeks. Other covariate information was

collected from the mother's and child's EMR data. Details of these covariates are

described elsewhere[19] and in the supplemental material. Briefly, these included maternal

characteristics: age, education, race and ethnicity, asthma, allergies, smoking during

pregnancy, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational

hypertension, breastfeeding, prenatal antibiotics, and cesarean section; and child

characteristics: birth year, infant sex, parity, birth weight, neonatal intensive care unit

(NICU) admission, child's first year antibiotics, and child's BMI.

Statistical Analysis

Using modified Poisson regression models with robust variance estimation[22,23] we

estimated childhood asthma risk ratios (RR) and 95% CI for each follow-up age (4 and 6

years). Each metric of GWG was included separately as the main exposure and was

modeled continuously per 1 unit increase (total GWG [lbs.], first trimester GWG [lbs.],

second/third trimester GWG [lbs.], first trimester GWG rate [lbs./week], and second/third

trimester GWG rate [lbs./week]) or categorically (total GWG 10 lbs. categories and IOM

categories). All analyses were stratified by prepregnancy BMI categories: normal,

overweight, obese class 1, and obese class 2/3 (underweight was not included due to

small sample size). All models included *a priori* identified potential confounding

variables including gestational age, maternal characteristics (age, education, race/ethnicity), maternal asthma and allergies, smoking during pregnancy, birth year, infant sex, and parity. All other covariates (prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, cesarean section, birth weight, NICU admission, child's first year antibiotics, and child's BMI) were evaluated as potential confounders and/or intermediates. As shown in the example DAG in the supplemental material (Figure S1; created using DAGitty[18]) these covariates could both confound the association between GWG and childhood asthma (through backdoor pathways) or act as intermediates on the pathway between GWG and childhood asthma.

Sensitivity analyses

As the childhood asthma outcome definition was designed to prioritize high specificity (minimize false positives), which is ideal for minimizing bias in the RR; a secondary, less stringent childhood asthma definition was examined in sensitivity analyses (see supplemental material for outcome definition). Additional sensitivity analyses included (1) IOM categories redefined according to recommended ranges of total GWG that ignore gestational age at delivery (where adequate total GWG was 28-40 lbs. for underweight BMI, 25-35 lbs. for normal BMI, 15-25 lbs. for overweight BMI, and 11-20 lbs. for all obese BMI classes), (2) adjustment for first trimester GWG in second/third trimester GWG models, (3) adjustment for first trimester GWG rate in second/third trimester GWG rate models, and (4) limited to full-term pregnancies ($\geq$37 weeks) only.

Parametric G-Formula

We implemented the parametric g-formula to estimate the risk of childhood asthma for each follow-up age (4 and 6 years) after standardizing the time-varying exposure GWG and time-varying confounding by gestational age. This involved three steps. First, using the observed EMR data, we fit models to predict the odds of remaining pregnant and the amount of weight gained for each mother-child pair for each gestational week. We also fit models to predict whether the child was diagnosed with asthma for each mother-child pair, but only for the final week of gestation (since all outcome measurements occurred after pregnancy follow-up time ended). These models included fixed covariates (maternal age, education, race/ethnicity, asthma, and allergies, smoking during pregnancy, birth year, infant sex, and parity) as well as time-specific predictors such as cumulative weeks pregnant and cumulative weight gained. Second, based on these models, we created a pseudo-cohort (using Monte Carlo sampling with replacement; n=50,000) which simulated the observed cohort's GWG and gestational age for each mother-child pair each week of gestation, incorporating GWG and gestational age from the previous week, and childhood asthma risk for each mother-child pair their final week of gestation (week they were born). Third, we estimated the risk of childhood asthma under the natural course (no intervention) using observed fixed covariates (maternal age, education, race/ethnicity, asthma, and allergies, smoking during pregnancy, birth year, infant sex, and parity) and the weighted cumulative GWG and cumulative weeks pregnant (gestational age) from the pseudo-cohort. Additional details of assumptions, algorithm used, and models are provided in the supplemental material.

The University of Nevada, Reno and KPNC Institutional Review Boards (IRB) approved all study protocols. Consent was provided by all KPNC members (upon

enrollment) to use their EMR data for medical research. Also, the reporting guideline

checklist for observational research using routinely collected data (RECORD)[24] was

completed for this study.[19] All analyses were completed in SAS 9.4 (SAS Institute, Cary,

NC).

Results

In the age 4 and 6 follow-up analyses, 93,389 and 57,808 children were included.

Among them 5.3% and 7.8% met the outcome asthma definition (Table 1). For both

follow-up ages, around half of mothers had a normal prepregnancy BMI, 27% had an

overweight prepregnancy BMI, 13% had an obese class 1 prepregnancy BMI, and 9%

had an obese class 2/3 prepregnancy BMI (Table 1). The strongest predictors of

childhood asthma were prepregnancy obesity (class 1 and 2/3), age (<25 years), race

(Black), active asthma, allergies, infant sex (male) and gestational age (<37 weeks).

Table 2 shows the different GWG metrics evaluated in the models stratified by

prepregnancy BMI.

Total GWG

Total GWG RRs and 95% CIs from models adjusted for *a priori* confounders

(maternal age, education, race/ethnicity, asthma, and allergies, smoking during

pregnancy, birth year, infant sex, parity, gestational age) and stratified by prepregnancy

BMI categories (normal, overweight, obese class 1 and obese class 2/3) are presented in

Table 3 for the age 4 and 6 year follow-up age analyses. The RR for a 1 lb. increase in

total GWG showed no association with childhood asthma for any prepregnancy BMI

category or follow-up age. This lack of association persisted when total GWG was

modeled categorically using 10 lbs. categories (reference = 20-29 lbs.) and IOM

categories. The only exceptions were (1) in the age 4 analysis there was a 32% decrease

in asthma risk among children born to mothers who had an obese class 1 prepregnancy

BMI and gained 40-49 lbs. during their pregnancy (RR=0.68, 95% CI=0.51, 0.91), (2) in

the age 6 analysis gaining 40-49 lbs. during pregnancy among mother-child pairs who

had a normal prepregnancy BMI was also associated with increased risk of childhood

asthma (RR=1.17, 95% CI=1.03, 1.33), and (3) in the age 6 analysis there was a 11%

significant increase in asthma risk among children born to mothers who had a normal

prepregnancy BMI and gained excessive weight during their pregnancy (RR=1.11, 95%

CI=1.01, 1.23). Some covariates were individually evaluated as potential confounders

and/or intermediates. These included: prepregnancy diabetes, gestational diabetes,

chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics,

cesarean section, birth weight, NICU admission, child's first year antibiotics, and child's

BMI. None of these covariates had any impact on GWG RRs and were therefore not

included in final models. Sensitivity analyses including the secondary childhood asthma

definition, redefined IOM categories, and limited to full-term pregnancies (≥37 weeks),

produced results very similar to the main analysis (not shown).

Trimester-specific GWG

Table 3 also shows the trimester-specific adjusted RRs and 95% CIs stratified by

prepregnancy BMI categories for follow-up ages 4 and 6 years. The RRs for a 1 lb.

increase in GWG in the first or second/third trimester show a predominately null

association with childhood asthma for any prepregnancy BMI category and follow-up

age. This is also seen for trimester-specific rate metrics save for a few notable exceptions.

In the age 4 analysis, there was a 12-14% increase in asthma risk, per 1 lb./week increase

in the first trimester GWG rate, among children born to mothers who had a normal or overweight prepregnancy BMI (RR=1.12, 95% CI=1.04, 1.21 and RR=1.14, 95% CI=1.06, 1.23, respectively). This pattern was also seen in the age 6 analysis (first trimester GWG rate, normal BMI: RR=1.18, 95% CI=1.09, 1.28 and overweight BMI: RR=1.09, 95% CI=1.01, 1.18). None of the covariates that were individually evaluated as potential confounders and/or intermediate changed GWG RRs and were not included in final models. Sensitivity analyses including the secondary childhood asthma definition, adjustment for first trimester GWG (total and rate) in second/third trimester models (total and rate), and only among full-term pregnancies (≥37 weeks), showed very similar results to the main analysis (not shown).

Parametric g-formula

Results from implementing the parametric g-formula are presented in Table 4. These RRs and 95% CI were estimated under the natural course (no intervention), using observed fixed covariates (maternal age, education, race/ethnicity, asthma, and allergies, smoking during pregnancy, birth year, infant sex, and parity) to control for baseline confounding, and the weighted cumulative GWG and cumulative weeks pregnant (gestational age) from each week in the pseudo-cohort to control for time-varying confounding. These results are largely compatible with the main analyses presented above though no GWG metric shows a significant association with childhood asthma for any prepregnancy BMI category or follow-up age.

Discussion

In this study we examine the association between GWG, using several different metrics, and childhood asthma among 100,000 mother-child pairs followed for at least 4

years after birth. There was largely no association detected between GWG and childhood asthma in any of the prepregnancy BMI categories, and these patterns persisted through multiple sensitivity analyses and after implementing the parametric g-formula (natural course) to account for time-varying confounding by pregnancy duration. We did observe a significant increase in childhood asthma risk with increasing first trimester GWG rate among children born to mothers with normal or overweight prepregnancy BMIs. However, considering this was for a relatively large increase in GWG rate, 1 lb./week in the first trimester (normal BMI standard deviation [SD]=0.5, overweight BMI SD=0.6, for both age 4 and 6 years), the elevated risk in childhood asthma is rather modest. There were other isolated significant results, though these should be considered in the context of many comparisons made for several different GWG metrics.

While a clear association exists between prepregnancy obesity and childhood asthma, fewer studies have investigated the role of GWG in childhood asthma development. This could be due to the methodological challenges in collecting GWG information throughout pregnancy and analytical issues with using multiple or single measurements of GWG.[17] There is also a lack of consensus on what GWG metric should be used and which methods appropriately account for confounding bias created by pregnancy duration,[15] which if ignored could induce a false association between low GWG and childhood asthma, as those with shorter pregnancy duration (preterm births) have less opportunity to gain weight.

Previous studies that have investigated this association present inconsistent and sometimes conflicting results. While both meta-analyses on this topic reported that higher GWG was associated with increased childhood asthma risk, one found that low GWG

was also associated with higher risk of childhood asthma,[4] and the other did not.[25] Evidence for a positive association between GWG and childhood asthma is found in several individual studies,[5–7] though other, one more recent, examples show no association.[9,10] Our analysis primarily showed null associations between GWG and childhood asthma, except for a positive association between first trimester GWG rate and childhood asthma among mother-child pairs who had normal or overweight prepregnancy BMI. Although similar results have not been seen in studies assessing asthma outcomes, Leermakers et al., investigated the effect of total GWG on preschool wheezing (among children aged 1-4 years) and found that the effect of total GWG (per standard deviation [4.7 kg] increase) on wheezing was strongest among children whose mothers had normal or overweight prepregnancy BMIs (normal BMI: OR=1.08, 95%CI=1.01, 1.15), overweight BMI: OR=1.18, 95%CI=1.06, 1.31).[26]

Although consideration of pregnancy duration is critical when evaluating GWG as an exposure (in that the longer a woman is pregnant the more weight she has the opportunity to gain),[15,17] it is often unaccounted for in previous studies.[6,8] Adjustment for prepregnancy BMI when estimating main effects from GWG is typically included in previous studies.[5–8,10] Even though there is evidence to suggest that childhood asthma risk differs depending on maternal prepregnancy BMI, stratified analyses are rarely considered.[7] GWG is also inconsistently operationalized in previous work, which makes comparisons difficult. All previous studies include total GWG (delivery weight – prepregnancy weight), though some use it as a continuous variable,[7] 10 lbs. categories,[6–8] categories according to IOM guidelines,[7,9,10] or a weekly rate.[7] No previous works included serial measurements of GWG.

This study included 100,000 mother-child pairs, making it the largest study in the United States to investigate the relationship between GWG and childhood asthma. We used EMR data, which included prospectively collected serial weight measurements throughout pregnancy, and routinely collected medication dispensing and diagnostic data. It also allowed for the inclusion of several covariates related to both the mother and the child, often absent from previous work. Childhood asthma was determined using a combination of ICD 9/10 codes and prescription asthma-related medication dispensings, at multiple follow-up ages. Multiple GWG metrics were included using both a single summary measure and multiple serial measurements, including total GWG (continuous, 10 lbs. categories, and IOM categories), and trimester-specific GWG (total and weekly rates). The relationship between GWG and pregnancy duration was considered, and each analysis included control for confounding by gestational age. Additionally, all analyses were stratified by prepregnancy BMI, to potentially highlight different effects of GWG on childhood asthma for each prepregnancy BMI category, and control for any differences in confounding between prepregnancy BMI categories. We also implemented the parametric g-formula to control time-varying confounding by gestational age while estimating the association between our time-varying exposure GWG and childhood asthma.

While many confounding variables were considered and adjusted for in these analyses, it is possible that there is residual confounding, due to poorly measured or unmeasured factors (e.g., genetics, lifestyle factors, or environment). Prepregnancy weight and prepregnancy BMI calculations included weight measurements up to 10 weeks into pregnancy (for some women), which may lead to misclassification as some

women may have already started gaining weight. However, weight gain in the first

trimester is typically small, between 1 and 4 lbs.[12] Calculating weekly rates of GWG

linearly ignores the fact that weight gain throughout pregnancy is likely not linear. We

know weight gain trajectories are different in the first trimester compared to the second

and third trimester,[26] so to account for this we calculated trimester-specific weekly GWG

rates. There was also potential for outcome misclassification as EMR data and algorithms

were used to determine asthma status at each follow-up age. Though, the magnitude of

bias in the RRs reported would be driven by false positives and our stringent outcome

definition was designed to minimize such false positives (children without asthma being

misclassified as having asthma).[27(p359)] Additionally, our secondary asthma outcome

definition yielded similar results to our primary asthma outcome definition. Another

limitation could be that the study population represents a fully-insured cohort of mother-

child pairs that may not be generalizable to other populations. Although, the availability

of comprehensive diagnosis and prescription medication histories was a strength of this

study. Finally, mother-child pairs with missing data were excluded from this study and

some women were excluded from trimester-specific GWG analyses because they did not

have enough weight measurements, which could result in selection bias. Though missing

data and early pregnancy weight measurements were not related to any other study

variables except birth year (reflecting gradual adoption of EMR over time).[19] While

implementing the parametric g-formula was a strength of this study, this method is

subject to limitations such as identifiability assumptions violations,[28] potentially

misspecified parametric models,[16] and the g-null paradox (where model misspecification

is guaranteed when exposure-confounder feedback is present) which can lead to falsely

rejecting the null hypothesis (that exposure has no effect on the outcome.[29] Though our results mainly show no association between GWG (exposure) and childhood asthma (outcome).

Results from this study highlight a predominately null association between GWG and childhood asthma, even when controlling for time-varying confounding. Though we did observe a modest positive association between first trimester GWG rate and childhood asthma risk (among mother-child pairs with normal or overweight prepregnancy BMIs), this should be considered in the context of multiple comparisons made for several metrics of GWG. Nonetheless future studies could follow up on this result. If replicated, it may be a consideration in recommendations for GWG by prepregnancy BMI category. With increases in childhood asthma, prepregnancy obesity, and excessive GWG continuing, exploration of inflammatory and other biological mechanisms and potential interventions is important.

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Figure 4.1 Directed acyclic graph (DAG) showing relationship between time-varying

exposure gestational weight gain (GWG) and time-varying confounder gestational age
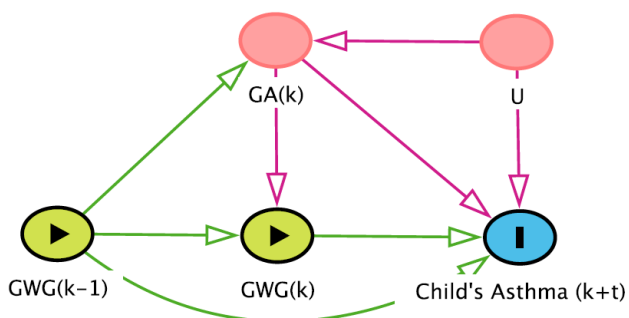
Abbreviations: GWG – gestational weight gain, GA – gestational age
Legend:
Exposure = GWG
Outcome = child's asthma
Green arrow = causal pathway
Pink arrow = biasing pathway

Notes: In the above figure, GWG(k) is the cumulative GWG at time point k. GWG(k-1) is the previous week's cumulative GWG. GA(k) is the cumulative weeks pregnant (gestational age) at time point k. Child's asthma (k+t) is the outcome measured some time after pregnancy follow-up has ended. U is some unmeasured confounder between gestational age and child's asthma (e.g., genetics). The association between cumulative gestational weight gain (GWG) at time point k (week of pregnancy) and childhood asthma (measured after follow-up: k+t) is confounded by actively being pregnant that week (or cumulative gestational age), due to the pathway GWG(k) <- GA(k) -> Child's Asthma (k+t) and GWG(k) <- GA(k) <- U -> Child's Asthma (k+t). Conditioning on gestational age at time point k is not adequate because actively being pregnant is affected by previous exposure (last week's cumulative GWG). Blocking this confounding pathway (selection bias) will then open a backdoor path GWG(k-1) -> GA(k) <- U -> Child's Asthma (k+t).

Table 4.1: Maternal and child characteristics for follow-up ages 4 and 6 years

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N
Total	4968 (5.3)	93389	4522 (7.8)	57808
Prepregnancy BMI[a] (kg/m^2)				
Normal	2261 (4.7)	47632	2029 (6.9)	29556
Overweight	1426 (5.5)	25838	1296 (8.2)	15858
Obese 1	721 (6.1)	11740	669 (9.2)	7291
Obese 2&3	560 (6.5)	8179	528 (10.3)	5103
Age (years)				
<25	505 (6.4)	7898	466 (9.4)	4973
25-29	1293 (5.2)	25043	1160 (7.3)	15788
30-34	1893 (5.4)	35300	1639 (7.9)	21417
35-39	1022 (5.1)	20234	1003 (8.0)	12507
≥40	255 (5.2)	4914	254 (8.1)	3123
Education (years)				
<12	188 (5.7)	3281	191 (8.9)	2155
12-15	2274 (5.9)	38421	2179 (8.9)	24615
16+	2506 (4.8)	51687	2152 (6.9)	31038
Race/Ethnicity				
White	1788 (4.4)	40692	1578 (6.3)	25197
Black	471 (8.9)	5279	401 (12.2)	3281
API	1387 (5.4)	25861	1311 (8.3)	15853
Hispanic	1283 (6.3)	20296	1207 (9.2)	13159
Other	39 (6.6)	593	25 (7.9)	318
Asthma[b]				
Active	1126 (9.3)	12138	1034 (14.4)	7183
Past	435 (7.0)	6191	415 (10.6)	3922
None	3407 (4.5)	75060	3073 (6.6)	46703
Allergies[c]				
Yes	3018 (6.4)	47437	2874 (9.4)	30443
No	1950 (4.2)	45952	1648 (6.0)	27365
Smoking During Pregnancy				
Yes	497 (5.8)	8530	410 (8.3)	4936
No	4471 (5.3)	84859	4112 (7.8)	52872
Infant Sex				
Male	3172 (6.7)	47680	2854 (9.7)	29498
Female	1796 (3.9)	45709	1668 (5.9)	28310
Parity				
First Born	2053 (5.0)	41071	1896 (7.6)	24864
Second Born	1925 (5.6)	34110	1718 (8.1)	21176
Third Born +	990 (5.4)	18208	908 (7.7)	11768
Gestational Age (weeks)				
<32	103 (16.6)	621	83 (23.0)	361
32	26 (10.8)	240	19 (12.5)	152
33	36 (9.9)	364	30 (14.4)	208
34	65 (9.0)	726	62 (14.1)	441
35	105 (8.5)	1241	88 (11.0)	799
36	227 (8.5)	2658	195 (11.4)	1710
37	431 (6.5)	6655	381 (9.3)	4083
38	848 (5.4)	15647	805 (8.1)	9977
39	1659 (5.3)	31449	1493 (7.8)	19245
40	1055 (4.5)	23208	956 (6.7)	14316
≥41	413 (3.9)	10580	410 (6.3)	6516

Abbreviations: BMI – body mass index

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30.0 – 34.9 kg/m^2), and obese class 2/3 (≥35 kg/m^2)

[b]Asthma during this pregnancy determined using diagnoses reported on medical intake forms and medication dispensing

[c]Maternal allergies including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the electronic medical record

Table 4.2: Gestational weight gain metrics for follow-up ages 4 and 6 years, by prepregnancy body mass index category

| | Prepregnancy BMI[a] | | | |
	Normal	Overweight	Obese Class 1	Obese Class 2/3
Categorical GWG Metrics	Total (% asthma)	Total (% asthma)	Total (% asthma)	Total (% asthma)
Age 4				
10 lbs. Categories				
<10 lbs.	688 (4.9)	1493 (4.7)	1610 (6.3)	2225 (7.8)
10-19 lbs.	4556 (5.3)	4335 (6.5)	2681 (6.5)	1992 (7.0)
20-29 lbs.	14932 (4.5)	7522 (5.3)	3202 (6.3)	1873 (6.1)
30-39 lbs.	16494 (4.6)	6853 (5.4)	2245 (6.4)	1195 (6.7)
40-49 lbs.	7811 (5.1)	3595 (5.2)	1220 (4.3)	538 (6.1)
≥ 50 lbs.	3151 (5.0)	2040 (5.8)	782 (6.0)	356 (6.0)
IOM Categories[b]				
Inadequate	7318 (4.7)	2845 (5.3)	1927 (6.1)	2541 (7.8)
Adequate	14192 (4.5)	4897 (5.6)	1528 (5.7)	1148 (7.5)
Excessive	26122 (4.9)	18096 (5.5)	8285 (6.2)	4490 (6.1)
Age 6				
10 lbs. Categories				
<10 lbs.	438 (5.9)	897 (7.2)	975 (9.4)	1377 (11.5)
10-19 lbs.	2718 (6.9)	2682 (8.7)	1631 (10.4)	1264 (9.7)
20-29 lbs.	9102 (6.5)	4612 (7.9)	1997 (9.1)	1153 (9.6)
30-39 lbs.	10365 (6.8)	4171 (8.6)	1452 (8.9)	747 (10.7)
40-49 lbs.	4937 (7.5)	2228 (8.1)	761 (8.4)	342 (11.1)
≥ 50 lbs.	1996 (7.5)	1268 (7.3)	475 (7.2)	220 (8.2)
IOM Categories[b]				
Inadequate	4410 (6.2)	1737 (7.5)	1168 (9.5)	1579 (11.3)
Adequate	8681 (6.5)	3072 (8.1)	924 (9.7)	729 (9.9)
Excessive	16465 (7.2)	11049 (8.3)	5199 (9.0)	2795 (9.9)
Continuous GWG Metrics	Total mean(SD) [asthma mean(SD)]	Total mean(SD) [asthma mean(SD)]	Total mean(SD) [asthma mean(SD)]	Total mean(SD) [asthma mean(SD)]
Age 4				
Total GWG Continuous[c]	32.4 (11.2) [32.6 (11.6)]	29.9 (13.9) [29.8 (14.1)]	25.6 (15.4) [24.9 (15.0)]	19.7 (16.7) [18.2 (16.5)]
First Trimester Total GWG[c]	3.3 (5.8) [3.7 (6.0)]	2.6 (7.7) [3.5 (7.6)]	2.1 (8.9) [2.0 (9.3)]	0.8 (10.0) [0.4 (10.0)]
Second/Third Trimester Total GWG[c]	27.0 (8.7) [26.7 (9.0)]	25.6 (10.4) [24.8 (10.5)]	22.3 (11.5) [21.8 (11.7)]	18.2 (12.4) [17.1 (12.3)]
First Trimester GWG Rate[d]	0.3 (0.5)	0.2 (0.6)	0.2 (0.7)	0.1 (0.8)

	[0.3 (0.5)]	[0.3 (0.6)]	[0.1 (0.8)]	[0.0 (0.8)]
Second/Third Trimester GWG Rate[d]	1.1 (0.4)	1.1 (0.4)	0.9 (0.5)	0.8 (0.5)
	[1.1 (0.4)]	[1.1 (0.4)]	[0.9 (0.5)]	[0.7 (0.5)]
Age 6				
Total GWG Continuous[c]	32.5 (11.2)	29.9 (13.9)	25.7 (15.2)	19.7 (16.8)
	[33.2 (11.6)]	[29.7 (13.4)]	[24.8 (14.4)]	[19.0 (16.1)]
First Trimester Total GWG[c]	3.4 (5.9)	2.7 (7.6)	2.1 (8.9)	0.8 (10.0)
	[4.0 (5.9)]	[3.4 (7.4)]	[2.1 (8.5)]	[0.7 (9.4)]
Second/Third Trimester Total GWG[c]	27.0 (8.8)	25.5 (10.4)	22.3 (11.4)	18.3 (12.3)
	[27.0 (9.1)]	[24.7 (10.2)]	[21.7 (11.2)]	[17.9 (12.2)]
First Trimester GWG Rate[d]	0.3 (0.5)	0.2 (0.6)	0.2 (0.7)	0.1 (0.8)
	[0.3 (0.5)]	[0.3 (0.6)]	[0.2 (0.7)]	[0.1 (0.8)]
Second/Third Trimester GWG Rate[d]	1.1 (0.4)	1.1 (0.4)	0.9 (0.5)	0.8 (0.5)
	[1.2 (0.4)]	[1.1 (0.4)]	[0.9 (0.5)]	[0.8 (0.5)]

Abbreviations: BMI – body mass index, GWG – gestational weight gain, IOM – Institutes of Medicine

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30.0 – 34.9 kg/m^2), and obese class 2/3 ($\geq$35 kg/m^2)

[b]Weight gain adequacy determined by comparing observed GWG to expected GWG according to prepregnancy BMI specific IOM guidelines; expected GWG calculated by [recommended first trimester total weight gain + [(gestational age at weight measurement at or before delivery – 13 weeks) * recommended rate of gain in the second and third trimesters]; observed GWG was within the expected range was considered adequate, below was considered inadequate, and above was considered excessive

[c]Units in lbs.

[d]Units in lbs./week

Table 4.3: Adjusted risk ratios and 95% confidence intervals for gestational weight gain

metrics for follow-up ages 4 and 6

| | Prepregnancy BMI[a] | | | |
| | Normal | Overweight | Obese Class 1 | Obese Class 2/3 |
Age 4	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total GWG Continuous[b]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
10 lbs. Categories				
<10 lbs.	0.91 (0.66, 1.27)	0.79 (0.62, 1.01)	0.93 (0.74, 1.17)	1.20 (0.96, 1.50)
10-19 lbs.	1.10 (0.95, 1.26)	1.14 (0.98, 1.32)	0.98 (0.81, 1.19)	1.11 (0.88, 1.40)
20-29 lbs.	1.00 [Reference]			
30-39 lbs.	1.03 (0.93, 1.14)	1.03 (0.90, 1.17)	1.03 (0.84, 1.27)	1.09 (0.83, 1.43)
40-49 lbs.	1.13 (1.00, 1.28)	1.00 (0.85, 1.18)	**0.68 (0.51, 0.91)**	0.94 (0.65, 1.36)
≥ 50 lbs.	1.07 (0.90, 1.27)	1.14 (0.93, 1.38)	0.93 (0.68, 1.26)	0.88 (0.56, 1.38)
IOM Categories[c]				
Inadequate	1.04 (0.92, 1.18)	0.94 (0.78, 1.13)	1.09 (0.83, 1.42)	1.03 (0.81, 1.31)
Adequate	1.00 [Reference]			
Excessive	1.08 (0.99, 1.19)	0.98 (0.86, 1.12)	1.10 (0.89, 1.37)	0.80 (0.63, 1.00)
Trimester-Specific				
First Trimester Total GWG[d]	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)
Second/Third Trimester Total GWG[d]	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)
First Trimester GWG Rate[e]	**1.12 (1.04, 1.21)**	**1.14 (1.06, 1.23)**	0.95 (0.86, 1.05)	0.91 (0.83, 1.00)
Second/Third Trimester GWG Rate[e]	1.01 (0.90, 1.14)	0.96 (0.85, 1.08)	1.01 (0.87, 1.17)	0.90 (0.78, 1.04)
Age 6				
Total GWG Continuous[b]	1.01 (1.00, 1.01)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
10 lbs. Categories				
<10 lbs.	0.81 (0.56, 1.17)	0.83 (0.64, 1.07)	0.96 (0.76, 1.22)	1.17 (0.93, 1.47)
10-19 lbs.	0.99 (0.85, 1.17)	1.08 (0.92, 1.26)	1.07 (0.88, 1.30)	1.01 (0.79, 1.29)
20-29 lbs.	1.00 [Reference]			
30-39 lbs.	1.09 (0.98, 1.21)	1.13 (0.98, 1.30)	0.96 (0.78, 1.19)	1.17 (0.90, 1.52)
40-49 lbs.	**1.17 (1.03, 1.33)**	1.08 (0.91, 1.28)	0.91 (0.69, 1.18)	1.18 (0.84, 1.66)
≥ 50 lbs.	1.17 (0.98, 1.39)	0.94 (0.75, 1.18)	0.77 (0.54, 1.10)	0.85 (0.54, 1.34)
IOM Categories[c]				
Inadequate	0.95 (0.82, 1.09)	0.93 (0.76, 1.13)	0.98 (0.76, 1.27)	1.17 (0.90, 1.52)
Adequate	1.00 [Reference]			
Excessive	**1.11 (1.01, 1.23)**	1.03 (0.90, 1.18)	0.93 (0.75, 1.14)	1.02 (0.79, 1.31)
Trimester-Specific				
First Trimester Total GWG[d]	1.01 (1.00, 1.02)	1.01 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Second/Third Trimester Total GWG[d]	1.01 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
First Trimester GWG Rate[e]	**1.18 (1.09, 1.28)**	**1.09 (1.01, 1.18)**	0.95 (0.86, 1.04)	0.97 (0.89, 1.06)
Second/Third Trimester GWG Rate[e]	1.06 (0.94, 1.19)	0.97 (0.86, 1.10)	1.01 (0.87, 1.17)	1.02 (0.88, 1.18)

Abbreviations: BMI – body mass index, RR – risk ratio, CI – confidence interval, GWG – gestational weight gain, IOM – Institutes of Medicine
[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30.0 – 34.9 kg/m^2), and obese class 2/3 (≥35 kg/m^2)
[b]RRs presented per 1 unit (lbs.) increase
[c]Weight gain adequacy determined by comparing observed GWG to expected GWG according to prepregnancy BMI specific IOM guidelines; expected GWG calculated by [recommended first trimester total weight gain + [(gestational age at weight measurement at or before delivery – 13 weeks) * recommended rate of gain in the second and third trimesters]; observed GWG was within the expected range was considered adequate, below was considered inadequate, and above was considered excessive.
[d]RRs presented per 1 unit (lbs.) increase
[e]RRs presented per 1 unit (lbs./week) increase

Table 4.4: Adjusted risk ratios and 95% confidence intervals for gestational weight gain

operationalizations for follow-up cohorts ages 4 and 6 from parametric g-formula natural

course

	Prepregnancy BMI[a]			
	Normal	Overweight	Obese Class 1	Obese Class 2/3
Age 4	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total GWG Continuous[b]	1.03 (1.00, 1.06)	1.02 (0.99, 1.04)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
10 lbs. Categories				
<10 lbs.	0.85 (0.56, 1.14)	0.87 (0.72, 1.05)	1.01 (0.89, 1.15)	1.02 (0.92, 1.13)
10-19 lbs.	1.10 (0.94, 1.29)	0.99 (0.88, 1.11)	1.10 (0.99, 1.23)	1.08 (0.98, 1.20)
20-29 lbs.	1.00 [Reference]			
30-39 lbs.	1.00 (0.90, 1.11)	0.97 (0.87, 1.07)	1.15 (1.03, 1.28)	1.05 (0.93, 1.18)
40-49 lbs.	0.99 (0.86, 1.13)	1.01 (0.89, 1.15)	1.04 (0.91, 1.19)	1.04 (0.89, 1.21)
≥ 50 lbs.	1.18 (0.99, 1.40)	1.03 (0.88, 1.20)	0.96 (0.81, 1.13)	0.94 (0.78, 1.14)
IOM Categories[c]				
Inadequate	1.03 (0.90, 1.18)	0.98 (0.84, 1.13)	0.88 (0.77, 1.00)	0.96 (0.86, 1.07)
Adequate	1.00 [Reference]			
Excessive	0.99 (0.90, 1.09)	1.04 (0.94, 1.15)	0.89 (0.80, 1.00)	0.95 (0.86, 1.06)
Trimester-Specific				
First Trimester Total GWG[d]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)
Second/Third Trimester Total GWG[d]	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.00)
First Trimester GWG Rate[e]	1.04 (0.95, 1.14)	1.04 (0.98, 1.10)	1.03 (0.98, 1.08)	0.98 (0.94, 1.02)
Second/Third Trimester GWG Rate[e]	1.05 (0.93, 1.19)	1.04 (0.95, 1.14)	0.95 (0.88, 1.03)	1.02 (0.96, 1.10)
Age 6				
Total GWG Continuous[b]	1.03 (1.00, 1.05)	1.01 (0.99, 1.03)	0.99 (0.98, 1.01)	1.02 (1.00, 1.04)
10 lbs. Categories				
<10 lbs.	0.72 (0.42, 1.02)	1.06 (0.92, 1.22)	1.00 (0.90, 1.10)	1.01 (0.93, 1.09)
10-19 lbs.	1.07 (0.94, 1.22)	0.98 (0.89, 1.08)	0.95 (0.88, 1.04)	1.00 (0.92, 1.09)
20-29 lbs.	1.00 [Reference]			
30-39 lbs.	1.01 (0.93, 1.11)	1.02 (0.94, 1.11)	0.97 (0.89, 1.06)	1.02 (0.93, 1.12)
40-49 lbs.	0.95 (0.85, 1.06)	1.08 (0.98, 1.20)	1.03 (0.92, 1.14)	0.90 (0.79, 1.03)
≥ 50 lbs.	1.03 (0.88, 1.19)	1.08 (0.95, 1.22)	0.91 (0.80, 1.04)	0.94 (0.80, 1.09)
IOM Categories[c]				
Inadequate	1.03 (0.92, 1.16)	1.01 (0.89, 1.13)	1.03 (0.93, 1.15)	1.02 (0.93, 1.12)
Adequate	1.00 [Reference]			
Excessive	1.01 (0.93, 1.09)	1.02 (0.94, 1.11)	1.03 (0.94, 1.13)	0.99 (0.91, 1.08)
Trimester-Specific				
First Trimester Total GWG[d]	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)
Second/Third Trimester Total GWG[d]	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
First Trimester GWG Rate[e]	1.00 (0.93, 1.08)	1.03 (0.98, 1.09)	0.99 (0.95, 1.03)	0.97 (0.94, 1.01)
Second/Third Trimester GWG Rate[e]	0.99 (0.89, 1.10)	1.04 (0.97, 1.12)	1.03 (0.97, 1.10)	0.97 (0.91, 1.02)

Abbreviations: BMI – body mass index, RR – risk ratio, CI – confidence interval, GWG – gestational weight gain, IOM – Institutes of Medicine

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30.0 – 34.9 kg/m^2), and obese class 2/3 (≥35 kg/m^2)

[b]RRs presented per 1 unit (lbs.) increase

[c]Weight gain adequacy determined by comparing observed GWG to expected GWG according to prepregnancy BMI specific IOM guidelines; expected GWG calculated by [recommended first trimester total weight gain + [(gestational age at weight measurement at or before delivery – 13 weeks) * recommended rate of gain in the second and third trimesters]; observed GWG was within the expected range was considered adequate, below was considered inadequate, and above was considered excessive.

[d]RRs presented per 1 unit (lbs.) increase

[e]RRs presented per 1 unit (lbs./week) increase

Chapter 5: Conclusion

This dissertation further investigated the association between prepregnancy body mass index (BMI) and risk of childhood asthma, evaluated potential intermediate factors between prepregnancy BMI and childhood asthma, and explored the role of gestational weight gain (GWG) on childhood asthma risk. Our study population was a retrospective cohort of births between 2005-2014 constructed using electronic medical records from over 100,000 mother-child pairs enrolled in Kaiser Permanente Northern California (KPNC), a large health maintenance organization. The studies contained in this dissertation also included careful consideration of methodological issues including mediation and time-varying confounding, and inclusion of many confounding factors often unaccounted for in the current literature. Additionally, these are the largest studies to date in the United States on this topic.

The current literature suggests there is evidence to support an effect of prepregnancy obesity on childhood asthma risk, through influences of the intrauterine environment. Our first study rigorously investigated the association between prepregnancy BMI and childhood asthma, including multiple follow-up ages (4, 6 and 8 years), two asthma outcome definitions, and continuous and categorical prepregnancy BMI metrics. Many potential confounding and intermediate variables, often absent in the current literature, were also included such as maternal characteristics: age, education, race and ethnicity, asthma, allergies, smoking during pregnancy, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, and cesarean section; and child characteristics: infant sex, parity,

birth weight, neonatal intensive care unit (NICU) admission, child's first year antibiotics, and child's BMI. Results showed an increased risk in childhood asthma as prepregnancy BMI increased. Risk ratios for prepregnancy BMI categories were similar in magnitude and direction across all follow-up ages and both asthma outcome definitions, though some were non-significant. After adjustment for important confounders (including GWG, gestational age, and child's own BMI), we still observed an increase in childhood asthma risk for higher prepregnancy BMI categories (overweight and all obese classes vs normal BMI).

Few studies have investigated mediating pathways between prepregnancy BMI and childhood asthma. In our first study we identified several candidate mediators and building off these results, we applied the causal inference test (CIT) and causal mediator models to test the potential mediating effects of GWG, gestational age, and child's BMI more formally. GWG did not meet the CIT conditions to be considered a mediator as excessive GWG was not associated with child's asthma. However, gestational age and child's BMI did meet the CIT conditions. In causal mediator models, child's BMI appeared to partially mediate the effect of prepregnancy BMI on childhood asthma, but no substantial evidence was observed for gestational age.

Often absent in the current literature addressing GWG and child outcomes, is the consideration of the relationship between GWG and gestational duration. Both are typically treated as time-fixed covariates, when in fact they are time-varying. Using summary measures, such as total GWG or gestational age at delivery, can result in biased estimates if the time-varying confounding feedback between GWG and gestational duration is not considered; especially if the outcome of interest is related to gestational

age, like childhood asthma. We investigated the association between GWG and childhood asthma, using different approaches to account for gestational age in our analyses. GWG was operationalized in several different ways including total GWG (continuous and categories), IOM recommended ranges of GWG, and trimester-specific GWG. We also implemented the parametric g-formula to account for the time-varying nature of GWG and to control for time-varying confounding by gestational age. The results from this study were predominantly null showing no association between GWG and childhood asthma, even after controlling for gestational age.

In conclusion, the findings from this dissertation offer supportive evidence to a causal link between prepregnancy obesity and childhood asthma development, a relationship that may partially be mediated through the child's own obesity. These findings did not show evidence of an effect of GWG on childhood asthma risk, even after stratifying by prepregnancy BMI and accounting for the time-varying confounding by gestational duration. Future research could focus on investigating potential mechanisms linking prepregnancy obesity and childhood asthma, including inflammatory markers, fetal microbiome changes, and immunological development. Additionally, thoughtful consideration of interventions on both prepregnancy obesity and childhood obesity are needed. This would not only positively impact women throughout their pregnancy but would also benefit their offspring in potentially reducing the risk of childhood asthma.

Appendix A: Electronic Medical Record Data Cleaning

Data cleaning
All datasets were read into and manipulated in SAS

Datasets (infant, mom height and weight, child height and weight) from KPNC were investigated using PROC CONTENTS, labels, and formats. Only the variables needed for data cleaning and analyses were kept. Some outcome variables (loose asthma) were renamed for easy identification. Maternal diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies were combined into a single variable indicating if the mother ever had any allergies at any time. Child's antibiotic use in the first week (yes/no) and child's antibiotic use from the second week up to the first year were combined into a single variable indicating if the child received antibiotics in their first year of life. Mothers who were missing a race/ethnicity (=99) were combined with the 'Other' category.

Maternal height
Mothers had several height measurements in their medical record. Only one measurement was needed to calculate prepregnancy BMI. The height measurement closest to conception date, but before conception, was used. If still missing, then the height measurement closest to conception date, any time in the record, was used.

Process: Read in maternal height and weight dataset and keep only height measurements (inches). Get rid of duplicate rows. Set implausible height values (<30 in or >84 in) to missing. Create variable for which gestational day height measurement was taken by subtracting the last menstrual period date (conception) from the date the measurement was taken (dates needed to be reformatted for calculation). Create variable for gestational week measurement was taken (gestational day divided by 7, then rounded down; if there were two or more measurements in the same week, only the first was used). Transpose the data to wide format. Select the measurement closest to conception date (prioritizing measurements taken before conception). This is used as the prepregnancy height measurement.

Maternal Weight
Mothers had several weight measurements in their medical record. A single weight measure for prepregnancy weight and delivery weight were needed to calculate prepregnancy BMI and total gestational weight gain. Additionally, weight measurements by gestational week needed to be identified.

Process: Read in maternal height and weight dataset and keep only weight measurements (lbs.). Get rid of duplicate rows. Set implausible weight values (<50 lbs. or >500 lbs.) to missing.
  - Some women had multiple weight measurements on the same day, so a single daily weight measurement needed to be selected. Data was transposed so each

row was a single day for each individual. A summary count variable indicating how many measurements were taken that day was created. Other variables created included: gestational day measurement was taken (measurement date – conception), gestational week measurement was taken (gestational day of measurement divided by 7, rounded down), gestational day of delivery (birth date – conception), gestational week of delivery (gestational day of delivery divided by 7, rounded down), a flag for if the weight measurement was taken on the delivery date (1=yes, 0=no), the difference between each measurement taken that day (ex: diff12 was the difference between the first measurement and the second measurement). Selection of weight measurement for that day:

- o If there was only one weight measurement taken that day, that measurement was used.
- o If there were two weight measurements taken that day, and they were within 10 lbs. of each other, an average was taken for that day. Else – see below
- o If there were three, four, or five weight measurements taken that day, and the difference between the first and last measurement was within 10 lbs. of each other, those measurements were averaged for that day. If not, then any two measurements that day that were within 10 lbs. of each other were used to create an average measure for that day. Else – see below
- o If the above was not met then weight measurements on that day were compared to weight measurements on surrounding days (3 before and 3 after); the weight measurement that day closest in value to the surrounding days' weight, but within the range of those measures (±1 lb.) was used

- Delivery weight
  - o if admission date was withing 3 days of delivery date, the weight measurement closest to the admission date was used
  - o OR any measurement within 7 days of delivery (closest to delivery date) was used

- Many women have multiple weight measurements in the same week of gestation – for analyses each only one weight measure for that gestational week is needed
  - o If there was only one weight measurement in that week, that measure was used
  - o If there were two or more weight measurements in that week, they were averaged
  - o Some outliers were influencing these averages so if an individual measurement was more than 5 lbs different from the average it was excluded from the average
  - o These single week measurements were also compared to surrounding week's measurements to highlight outliers
    - ▪ If there were two measurements that week and the average was inside the range of surrounding weeks' measurements use the average; if not set to missing

- If there were three or more measurements that week do not include the two most different weight measurements in the average calculation
- Prepregnancy weight
  - Weight measurement before conception (but closest), within 6 months, (also tried 3 months and 1 year) was used
  - If no weight measurement before conception, then use earliest weight measurement, up to 10 weeks into pregnancy
- Last weight measurement for pregnancy was replaced by delivery weight if it was different from delivery weight measurement
- Finally, simple linear regression models were used to identify any week-to-week outliers (x2)
- Week-to-week outliers were also identified when comparing to surrounding weeks' measurements (2 previous and 2 next)

Child's BMI

Process: Read in child height and weight dataset and combine with infant dataset for birthdates. Need to select a height and weight measurement for calculation of BMI categories using CDC child BMI-for-age percentiles

- For any given visit day use the height and weight measurement from that day
- If height and weight measurement not taken on same day, then can use closest height measurement within two months of weight measurement date
- Then data are set up to use with CDC SAS code: height units changed to cm, weight units changed to kg, create variable for months of age (at visit date: calculated as visit date – birth date, divided by 30), and child's sex. Then run CDC code: https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
- Select BMI (and percentile calculation) closest to previous birthday (within 6 months window) for each age: 4, 6, 8, 10

Datasets continuing maternal height, weight, and child's BMI variables were combined with the infant dataset (containing all other covariates)

I calculated the following before analyses:
- Gestational age in weeks = gestational days divided by 7, rounded down
- prepregnancy BMI = (prepregnancy weight / prepregnancy height^2)*703
- total GWG = delivery weight - prepregnancy weight
- prepregnancy BMI category (according to CDC)
  - underweight = BMI <18.5
  - normal = BMI 18.5 – 24.9
  - overweight = BMI 25.0 – 29.9
  - obese class 1 = BMI 30.0-34.9
  - obese class2/3 = BMI ≥35
- 10 lbs. categories of total GWG
- Total GWG IOM category (inadequate, adequate, excessive

- o Underweight adequate = 28-40 lbs.
- o Normal adequate = 25-35 lbs.
- o Overweight adequate = 15-25 lbs.
- o Obese (all classes) adequate = 11-20 lbs.
- Total GWG IOM category (accounting for gestational age at delivery)
  - o Underweight adequate = between $1.1+(gestage-13)*1.0$ and $4.4+(gestage-13)*1.3$
  - o Normal adequate = between $1.1+(gestage-13)*0.8$ and $4.4+(gestage-13)*1.0$
  - o Overweight adequate = between $1.1+(gestage-13)*0.5$ and $4.4+(gestage-13)*0.7$
  - o Obese (all classes) adequate = between $1.1+(gestage-13)*0.4$ and $4.4+(gestage-13)*0.5$
- Trimester specific GWG
  - o First trimester first weight = prepregnancy weight
  - o First trimester last weight between 10-13 weeks (or 14-16 if missing)
  - o Second/third trimester first weight between week 14-17 (or 12 if missing)
  - o Second/third trimester last weight = delivery weight
  - o Total GWG (in each trimester) = last weight minus first weight
  - o GWG rate (in each trimester) = total GWG (in each trimester) divided by number of weeks between first and last measure
- Child BMI percentile categories
  - o Underweight = $<5^{th}$
  - o Normal = 5th-85th
  - o Overweight = 85th-95th
  - o Obese = $>95^{th}$

Before analyses I set implausible values to missing: BMI<12 or BMI>81 and total GWG<-40 or total GWG>100

Appendix B: Supplemental Material for Prepregnancy Body Mass Index and Risk

of Childhood Asthma

Contents:

Table B1.1: The RECORD statement: checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract Abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract Abstract N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction		
Objectives	3	State specific objectives, including any prespecified hypotheses	Abstract, Introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods: Study Population		
Participants	6	*(a) Cohort study*- Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*- Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*- Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study*- For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*- For matched studies, give matching criteria and the number of controls per case	Abstract, Methods: Study Population N/A N/A N/A N/A	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods: Study Population N/A N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods: Exposure, Outcome, & Covariates	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods: Exposure, Outcome, & Covariates
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods		
Bias	9	Describe any efforts to address potential sources of bias	Methods, Discussion		
Study size	10	Explain how the study size was arrived at	Methods, Figure 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods: Statistical Analysis		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods: Statistical Analysis		
		(b) Describe any methods used to examine subgroups and interactions	Methods: Statistical Analysis		
			Methods		
		(c) Explain how missing data were addressed	Methods		
		(d) *Cohort study*- If applicable, explain how loss to follow-up was addressed	N/A		
		Case-control study- If applicable, explain how matching of cases and controls was addressed	N/A		
			Methods: Statistical Analysis		
		Cross-sectional study- If applicable, describe analytical methods taking account of sampling strategy			
		(e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Methods
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods: Exposure, & Covariates

Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	N/A
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Methods, Figure 1 Methods, Figure 1 Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Methods, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c)*Cohort study-* summarise follow-up time (*e.g.*, average	Results, Table 1, Table 2 Table 1, Table 2 Results, Table 1, Table 2		

		and total amount)			
Outcome data	15	*Cohort study*- Report numbers of outcome events or summary measures over time *Case-control study*- Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*- Report numbers of outcome events or summary measures	Results, Table 1, Table 2 N/A N/A		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, Discussion, Figure 3, Figure 4, Methods, Table 1, Table 2 N/A		

Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results		
Discussion					
Key results	18	Summarize key results with reference to study objectives	Discussion		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion		
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original	Funding statement		

		study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Online material statement, Results, Discussion

Notes: Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press. Checklist is protected under Creative Commons Attribution (CC BY) license.

B2. Tables

Table B2.1: Table S1: Child characteristics for follow-up ages 4, 6, and 8 (secondary

asthma definition)

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	8810 (6.5)	104467	7650 (12.1)	63084	4224 (13.6)	31006
Infant Sex						
Male	5619 (10.5)	53309	4688 (14.6)	32178	2587 (16.3)	15881
Female	3191 (6.2)	51158	2962 (9.6)	30906	1637 (10.8)	15125
Birth Weight						
<2500g	608 (13.7)	4440	497 (19.0)	2612	253 (20.3)	1246
2500-4000g	7198 (8.2)	88055	6291 (11.8)	53175	3480 (13.4)	26016
>4000g	1004 (8.4)	11972	862 (11.8)	7297	491 (13.1)	3744
Parity						
First Born	3540 (7.9)	45034	3195 (11.9)	26938	1770 (13.6)	13040
Second Born	3371 (8.8)	38092	2839 (12.3)	23081	1554 (13.6)	11388
Third Born +	1899 (8.9)	21341	1616 (12.4)	13065	900 (13.7)	6578
NICU Admission						
Yes	890 (12.8)	6937	764 (17.9)	4260	417 (19.6)	2127
No	7920 (8.1)	97530	6886 (11.7)	58824	3807 (13.2)	28879
First Year Antibiotics						
Yes	5221 (13.1)	39719	4340 (17.2)	25194	2391 (18.5)	12898
No	3589 (5.5)	64748	3310 (8.7)	37890	1833 (10.1)	18108
Child BMI (pct)[a]						
Underweight (<5th)	421 (9.0)	4698	287 (12.3)	2339	136 (14.5)	941
Normal (5th-84th)	5678 (8.2)	69169	4757 (11.5)	41353	2515 (14.2)	17676
Overweight (85th-95th)	1408 (10.1)	13975	1330 (14.0)	9523	651 (17.4)	3746
Obese (>95th)	1123 (12.4)	9036	1177 (17.7)	6650	701 (22.1)	3169
Missing	180 (2.4)	7589	99 (3.1)	3219	221 (4.0)	5474
Gestational Age (weeks)						
Mean [SD]	38.5 [2.1]	38.9 [1.7]	38.56 [2.1]	38.9 [1.7]	38.6 [2.0]	38.9 [1.7]

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

[a] Child BMI percentiles calculated using height and weight measurements within 6 months of previous birthday

Table B2.2: Table S2: Maternal characteristics for follow-up ages 4, 6, and 8 (secondary

asthma definition)

	Asthma Age 4 N (%)	Total Age 4 N	Asthma Age 6 N (%)	Total Age 6 N	Asthma Age 8 N (%)	Total Age 8 N
Total	8810 (8.4)	104467	7650 (12.1)	63084	4224 (13.6)	31006
Prepregnancy BMI[a]						
Underweight	164 (6.5)	2528	151 (10.1)	1500	88 (11.4)	771
Normal	3872 (7.5)	51845	3352 (10.7)	31402	1851 (12.0)	15427
Overweight	2517 (8.9)	28153	2170 (12.8)	16896	1188 (14.4)	8266
Obese 1	1282 (9.9)	12902	1097 (14.0)	7821	606 (15.7)	3870
Obese 2&3	975 (10.8)	9039	880 (16.1)	5465	491 (18.4)	2672
Mean [SD]	27.0 [6.3]	26.2 [5.9]	27.0 [6.3]	26.1 [5.9]	27.0 [6.4]	26.1 [5.9]
Age (years)						
Mean [SD]	30.9 [5.3]	31.3 [5.1]	31.1 [5.3]	31.3 [5.1]	31.0 [5.4]	31.2 [5.1]
Education						
<12	383 (10.5)	3660	338 (14.5)	2333	191 (15.4)	1240
12-15	4031 (9.3)	43201	3634 (13.6)	26723	2060 (15.1)	13625
16+	4257 (7.5)	56571	3588 (10.7)	33477	1930 (12.1)	15910
Missing	139 (13.4)	1035	90 (16.3)	551	43 (18.6)	231
Race/Ethnicity						
White	3132 (6.9)	45446	2693 (9.8)	27372	1525 (11.3)	13519
Black	827 (14.0)	5923	694 (19.2)	3611	407 (22.1)	1841
API	2405 (8.2)	29274	2168 (12.4)	17532	1144 (13.5)	8501
Hispanic	2379 (10.3)	23133	2047 (14.4)	14192	1138 (16.3)	7000
Other/Missing	67 (9.7)	691	48 (12.7)	377	10 (6.9)	145
Asthma[b]						
Active	1894 (14.3)	13246	1626 (21.1)	7690	843 (23.5)	3590
Past	775 (11.2)	6893	693 (16.3)	4240	409 (18.4)	2226
None	6141 (7.3)	84328	5331 (10.4)	51154	2972 (11.8)	25190
Allergies[c]						
Yes	5266 (10.1)	52237	4770 (14.5)	32852	2692 (16.1)	16720
No	3544 (6.8)	52230	2880 (9.5)	30232	1532 (10.7)	14286
Smoking During Pregnancy						
Yes	901 (9.4)	9573	728 (13.5)	5404	361 (14.5)	2491
No	7909 (8.3)	94894	6922 (12.0)	57680	3863 (13.5)	28515
Prepregnancy Diabetes						
Yes	244 (11.3)	2167	217 (16.2)	1337	138 (20.1)	688
No	8566 (8.4)	102300	7433 (12.0)	61747	4086 (13.5)	30318
Gestational Diabetes						
Yes	1235 (8.9)	13832	1069 (13.0)	8197	554 (15.2)	3648
No	7575 (8.4)	90635	6581 (12.0)	54887	3670 (13.4)	27358
Chronic Hypertension						
Yes	418 (11.1)	3754	393 (15.7)	2498	246 (19.4)	1270
No	8392 (8.3)	100713	7257 (12.0)	60586	3978 (13.4)	29736
Gestational Hypertension						
Yes	1194 (10.0)	11961	1042 (14.4)	7220	565 (16.8)	3370
No	7616 (8.2)	92506	6608 (11.8)	55864	3659 (13.2)	27636
Breastfeeding						

<3mo	2352 (9.6)	24457	1985 (13.0)	15297	1087 (14.3)	7625
3-6mo	1349 (9.2)	14660	1170 (12.8)	9126	608 (14.0)	4351
>6mo	4331 (7.5)	57576	3814 (11.3)	33770	2103 (12.8)	16414
None	759 (10.1)	7513	670 (14.1)	4738	416 (16.5)	2524
Missing	19 (7.3)	261	11 (7.2)	153	10 (10.9)	92
Prenatal Antibiotics						
Yes	3144 (10.5)	29991	2732 (14.8)	18407	1552 (16.9)	9158
No	5666 (7.6)	74476	4918 (11.0)	44677	2672 (12.2)	21848
Caesarean Section						
Yes	2687 (9.6)	27971	2376 (14.0)	17016	1324 (15.7)	8414
No	6123 (8.0)	76496	5274 (11.4)	46068	2900 (12.8)	22592
Total GWG[d]						
Inadequate	1825 (8.5)	21520	1510 (11.9)	12652	810 (13.2)	6147
Adequate	2759 (8.1)	34164	2392 (11.5)	20748	1328 (13.0)	10186
Excessive	4226 (8.7)	48783	3748 (12.6)	29684	2086 (14.2)	14673
Mean [SD]	29.3 [14.1]	29.7 [13.7]	29.4 [14.1]	29.9 [13.6]	29.8 [14.3]	30.0 [13.7]

Abbreviations: BMI – body mass index, GWG – gestational weight gain

[a]Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese class 1 (30 – 34.9 kg/m^2), obese class 2/3 (35+ kg/m^2)

[b]Asthma during this pregnancy determined using diagnoses reported on medical intake forms and medication dispensing

[c]Maternal allergies including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the electronic medical record

[d]Calculated as delivery weight minus prepregnancy weight; based on Institutes of Medicine recommend weight gain per prepregnancy BMI category

Table B2.3: Table S3: Adjusted risk ratios prepregnancy BMI categories (relative to Normal) and child's asthma, for different

GWG operationalizations for follow-up ages 4, 6, and 8

	Underweight		Overweight		Obese 1		Obese 2&3	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age 4								
Continuous Total GWG with Cubic Splines (final analysis)	0.91	(0.75, 1.11)	1.06	(0.99, 1.14)	1.09	(1.00, 1.19)	1.09	(0.99, 1.21)
(1) Continuous Total GWG	0.91	(0.75, 1.11)	1.07	(1.00, 1.14)	1.10	(1.01, 1.20)	1.10	(1.00, 1.21)
(2) Total GWG 10 lbs. Categories	0.91	(0.75, 1.11)	1.06	(0.99, 1.13)	1.09	(1.00, 1.18)	1.09	(0.99, 1.20)
(3) Total GWG IOM Categories	0.91	(0.75, 1.11)	1.06	(0.99, 1.14)	1.09	(1.00, 1.19)	1.09	(0.99, 1.20)
(4) Trimester Specific Total GWG	0.92	(0.75, 1.13)	1.07	(1.01, 1.15)	1.09	(1.00, 1.19)	1.07	(0.97, 1.19)
(5) Trimester Specific Total GWG with Cubic Splines	0.92	(0.75, 1.12)	1.08	(1.01, 1.15)	1.09	(1.00, 1.19)	1.08	(0.97, 1.19)
Age 6								
Continuous Total GWG with Cubic Splines (final analysis)	0.95	(0.78, 1.16)	1.08	(1.01, 1.16)	1.12	(1.03, 1.23)	1.13	(1.02, 1.25)
(1) Continuous Total GWG	0.95	(0.78, 1.16)	1.08	(1.01, 1.16)	1.12	(1.03, 1.22)	1.12	(1.01, 1.24)
(2) Total GWG 10 lbs. Categories	0.95	(0.78, 1.16)	1.08	(1.01, 1.16)	1.12	(1.03, 1.23)	1.12	(1.01, 1.24)
(3) Total GWG IOM Categories	0.96	(0.79, 1.17)	1.06	(0.99, 1.14)	1.10	(1.00, 1.20)	1.10	(1.00, 1.22)
(4) Trimester Specific Total GWG	0.93	(0.76, 1.14)	1.08	(1.00, 1.15)	1.12	(1.02, 1.22)	1.11	(1.01, 1.23)
(5) Trimester Specific Total GWG with Cubic Splines	0.92	(0.75, 1.13)	1.08	(1.01, 1.16)	1.13	(1.04, 1.24)	1.14	(1.02, 1.27)
Age 8								
Continuous Total GWG with Cubic Splines (final analysis)	0.97	(0.75, 1.27)	1.03	(0.94, 1.14)	1.03	(0.91, 1.17)	1.14	(0.99, 1.31)
(1) Continuous Total GWG	0.97	(0.75, 1.27)	1.04	(0.94, 1.14)	1.03	(0.91, 1.17)	1.14	(0.99, 1.31)
(2) Total GWG 10 lbs. Categories	0.97	(0.75, 1.27)	1.03	(0.94, 1.13)	1.03	(0.90, 1.16)	1.12	(0.97, 1.29)
(3) Total GWG IOM Categories	0.99	(0.76, 1.28)	1.01	(0.92, 1.11)	1.00	(0.88, 1.13)	1.10	(0.96, 1.25)
(4) Trimester Specific Total GWG	1.00	(0.77, 1.31)	1.04	(0.94, 1.14)	1.04	(0.91, 1.18)	1.10	(0.95, 1.26)
(5) Trimester Specific Total GWG with Cubic Splines	1.00	(0.76, 1.31)	1.05	(95, 1.15)	1.06	(0.93, 1.21)	1.13	(0.97, 1.31)

Abbreviations: BMI – body mass index, GWG – gestational weight gain, IOM – institutes of medicine

Note: Total GWG was calculated as delivery weight minus prepregnancy weight. 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.

Table B2.4: Table S4: Adjusted risk ratios for prepregnancy BMI (relative to Normal) and child's asthma from incident case analysis, for follow-up ages 4, 6, and 8.

|		Underweight		Overweight		Obese 1		Obese 2&3	
Primary Definition	Total N (% Asthma)	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age 4									
Unadjusted	104467 (5.0)	0.91	(0.75, 1.10)	1.16	(1.09, 1.24)	1.28	(1.18, 1.39)	1.44	(1.31, 1.57)
Adjusted†	95939 (5.3)	0.91	(0.75, 1.11)	1.06	(0.99, 1.14)	1.09	(1.00, 1.19)	1.10	(0.99, 1.21)
Alternative (asthma only at age 4)[a]	95939 (5.3)	0.91	(0.75, 1.11)	1.06	(0.99, 1.14)	1.09	(1.00, 1.19)	1.09	(0.99, 1.21)
Age 6									
Unadjusted	63084 (7.5)	0.98	(0.80, 1.19)	1.19	(1.11, 1.27)	1.32	(1.21, 1.44)	1.49	(1.36, 1.64)
Adjusted†	59359 (7.8)	0.95	(0.78, 1.16)	1.08	(1.01, 1.16)	1.12	(1.03, 1.23)	1.13	(1.02, 1.25)
Alternative (asthma only at age 6)[a]	58277 (8.0)	0.95	(0.78, 1.16)	1.08	(1.01, 1.16)	1.13	(1.03, 1.23)	1.13	(1.02, 1.25)
Age 8									
Unadjusted	31006 (8.1)	0.96	(0.74, 1.24)	1.15	(1.05, 1.26)	1.24	(1.11, 1.40)	1.50	(1.33, 1.70)
Adjusted†	25333 (9.4)	0.97	(0.75, 1.27)	1.03	(0.94, 1.14)	1.03	(0.91, 1.17)	1.14	(0.99, 1.31)
Alternative (asthma only at age 8)[a]	24162 (9.8)	0.97	(0.75, 1.27)	1.03	(0.94, 1.13)	1.04	(0.92, 1.18)	1.16	(1.01, 1.33)
All Ages									
Asthma at ages 4, 6, and 8[b]	19918 (3.5)	1.29	(0.83, 2.01)	1.14	(0.95, 1.37)	1.10	(0.86, 1.40)	1.23	(0.95, 1.60)
Secondary Definition	Total N (% Asthma)	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age 4									
Unadjusted	104467 (8.4)	0.86	(0.74, 1.00)	1.20	(1.14, 1.26)	1.33	(1.25, 1.41)	1.45	(1.35, 1.55)
Adjusted†	95939 (8.9)	0.84	(0.72, 0.98)	1.08	(1.02, 1.13)	1.12	(1.05, 1.19)	1.11	(1.03, 1.20)
Alternative (asthma only at age 4)[a]	95939 (8.9)	0.84	(0.72, 0.98)	1.08	(1.02, 1.13)	1.12	(1.05, 1.19)	1.11	(1.03, 1.20)
Age 6									
Unadjusted	63084 (12.1)	0.94	(0.81, 1.10)	1.20	(1.14, 1.27)	1.32	(1.23, 1.40)	1.51	(1.41, 1.62)
Adjusted†	59359 (12.6)	0.92	(0.79, 1.07)	1.10	(1.05, 1.16)	1.12	(1.05, 1.20)	1.15	(1.06, 1.25)
Alternative (asthma only at age 6)[a]	58211 (12.8)	0.91	(0.78, 1.06)	1.10	(1.04, 1.16)	1.12	(1.05, 1.20)	1.15	(1.06, 1.25)
Age 8									
Unadjusted	31006 (13.6)	0.95	(0.78, 1.16)	1.20	(1.12, 1.28)	1.31	(1.20, 1.43)	1.54	(1.40, 1.68)
Adjusted†	25333 (15.6)	0.96	(0.79, 1.18)	1.09	(1.02, 1.17)	1.12	(1.03, 1.23)	1.21	(1.09, 1.34)
Alternative (asthma only at age 8)[a]	24159 (16.4)	0.97	(0.79, 1.18)	1.09	(1.01, 1.17)	1.13	(1.03, 1.23)	1.22	(1.10, 1.36)
All Ages									
Asthma at ages 4, 6, and 8[b]	19659 (7.7)	1.01	(0.72, 1.40)	1.13	(1.00, 1.27)	1.16	(0.99, 1.35)	1.28	(1.07, 1.52)

Abbreviations: BMI – body mass index

[a]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 (within 6 months of previous birthday).
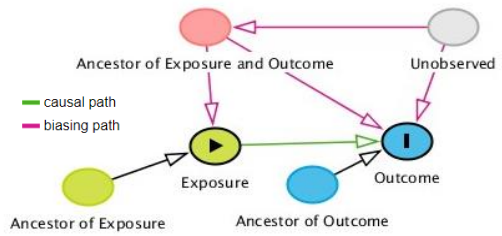
[b]Models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI (age 3, 5, and 7).

B3. Figures

Figure B3.1 Figure S1: Full directed acyclic graph used to identify confounding and mediating pathways between prepregnancy
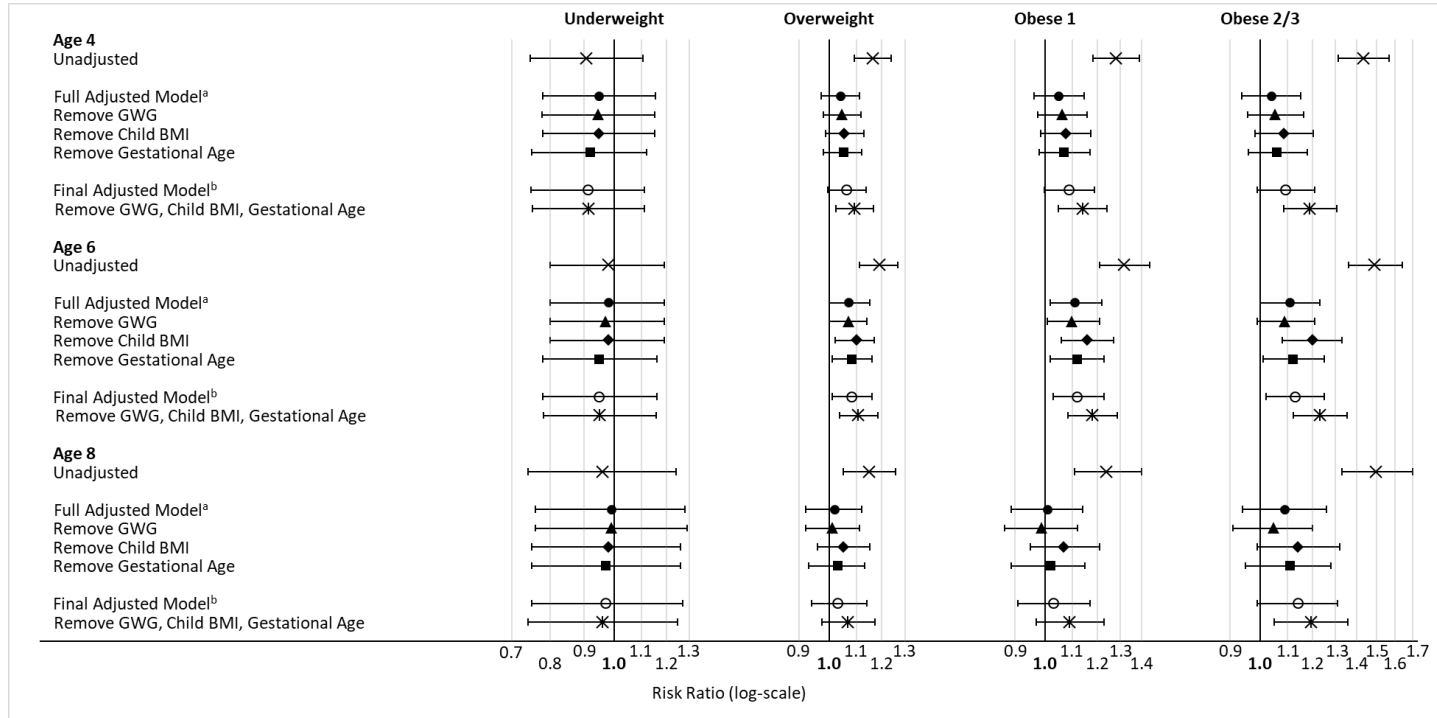
BMI and child's asthma
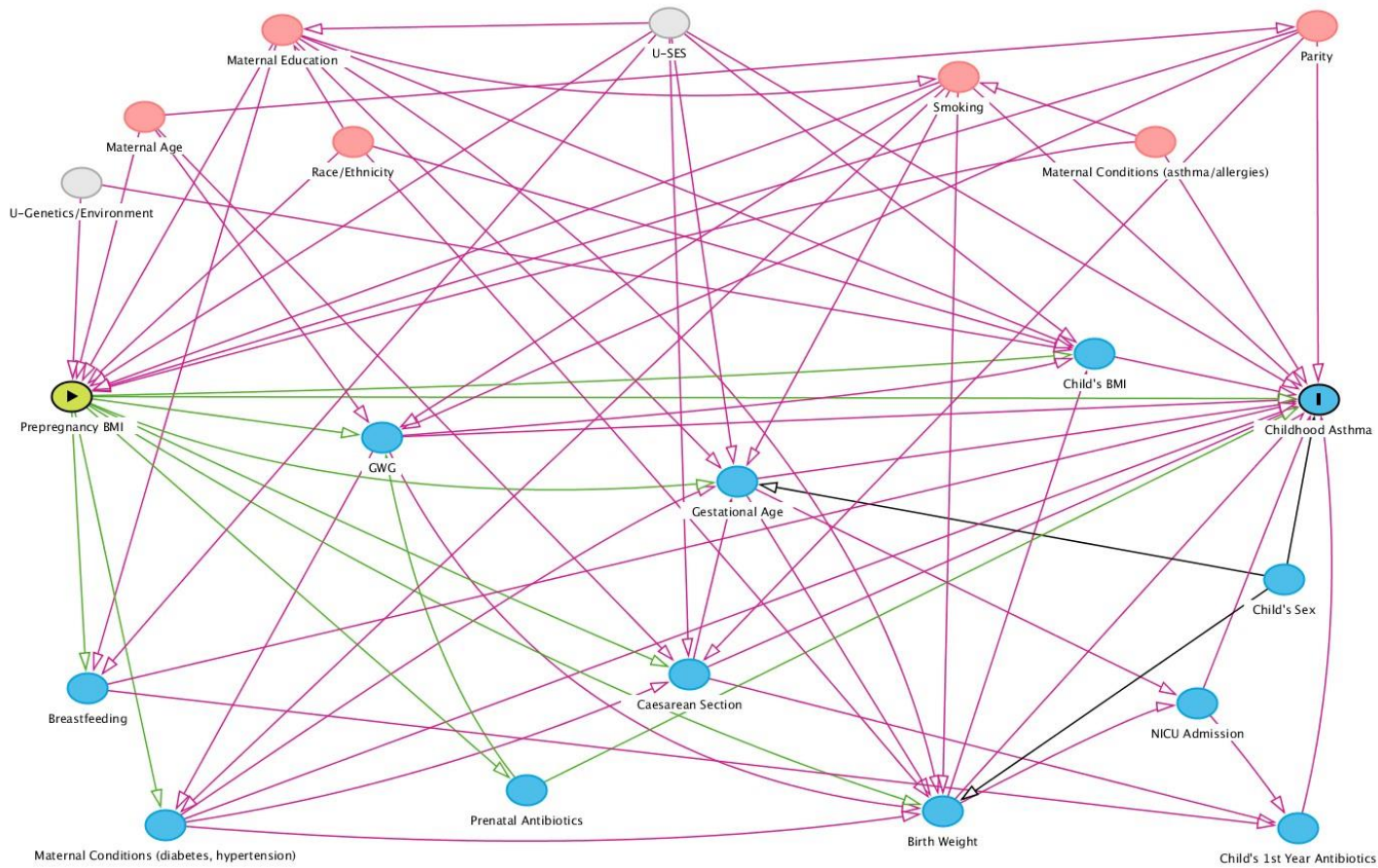
Legend:

Abbreviations:
BMI – body mass index
GWG – gestational weight gain
SES – socioeconomic status
NICU – neonatal intensive care unit

Figure B3.2: Figure S2: Unadjusted and adjusted risk ratios for prepregnancy BMI categories (relative to Normal) and child's

asthma for follow-up ages 4, 6, and 8, removing important confounding variables

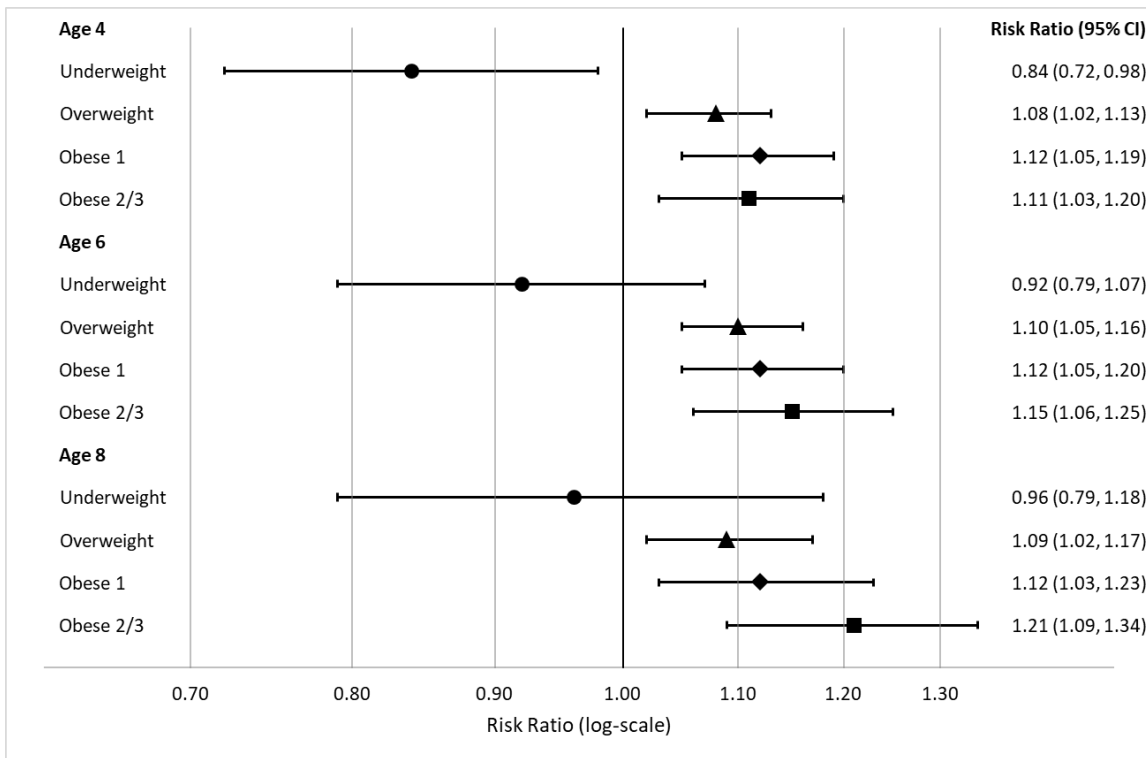Abbreviations: BMI – body mass index, GWG – gestational weight gain

[a]Fully adjusted models include maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, child's BMI, prepregnancy diabetes, gestational diabetes, chronic hypertension, gestational hypertension, breastfeeding, prenatal antibiotics, cesarean delivery, birth weight, neonatal intensive care unit (NICU) admission, and child's first year antibiotics.

[b]Final adjusted models are those presented in Figure 3 in main paper and include maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI.

Note: Prepregnancy BMI categories: underweight (<18.5 kg/m^2), normal ($18.5 – 24.9$ kg/m^2), overweight ($25.0 – 29.9$ kg/m^2), obese class 1 ($30 – 34.9$ kg/m^2), obese class 2/3 ($35+$ kg/m^2). Models including child BMI are based on N=95,939 (age 4), N=59,359 (age 6), N=25,333 (age 8). Models without child BMI are based on N=104,647 (age 4), N=63,084 (age 6), N=31,006 (age 8)

Figure B3.3: Figure S3: Adjusted risk ratios for prepregnancy BMI (relative to Normal) and child's asthma (secondary definition), for follow-up ages 4, 6, and 8

Abbreviations: BMI – body mass index

Notes: 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.

Figure B3.4: Figure S4: Adjusted risk ratios for continuous BMI (spline) and child's

asthma (secondary asthma definition), for follow-up ages 4, 6, and 8
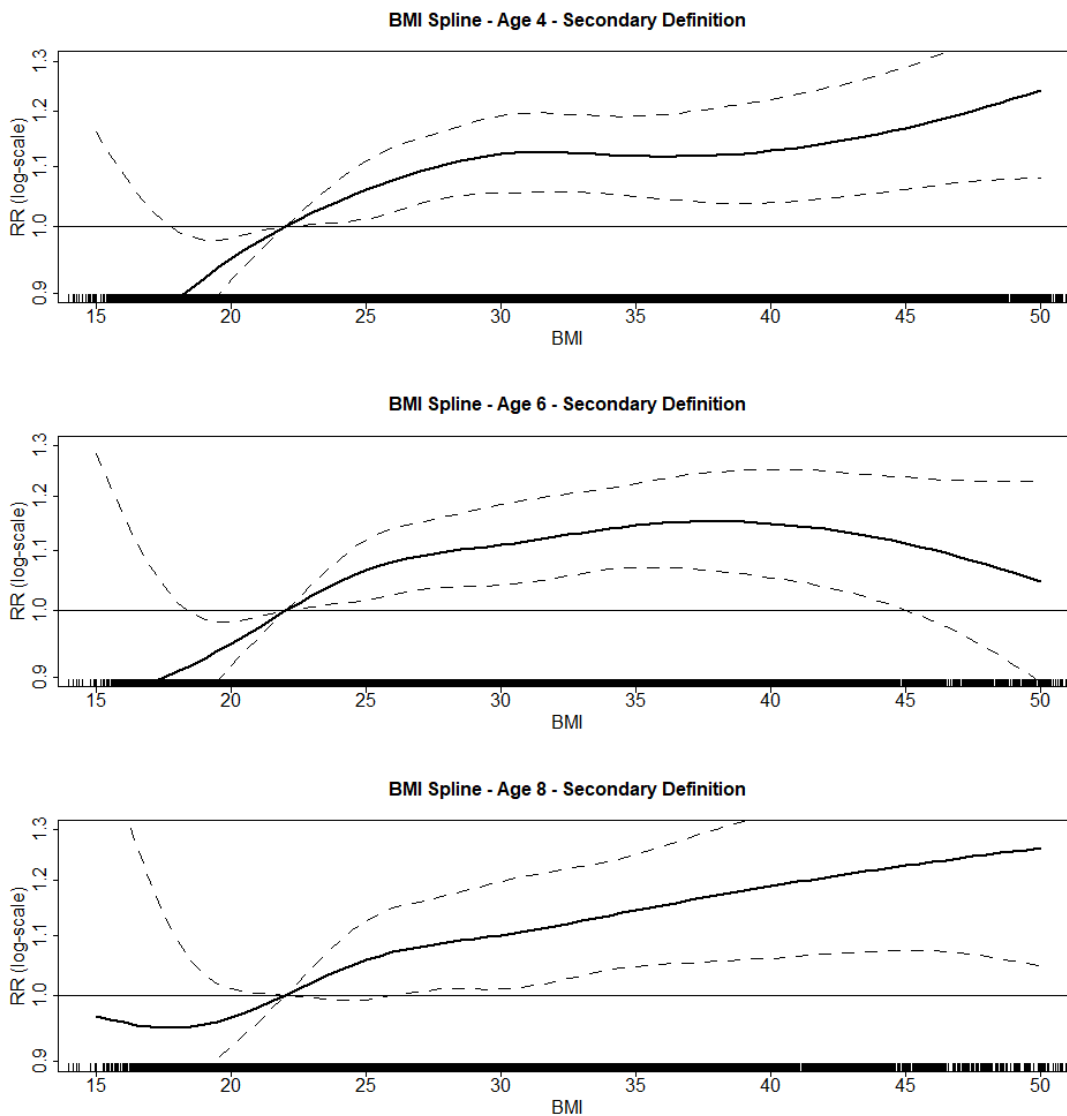
Abbreviations: RR – risk ratio, BMI – body mass index
Notes: All models adjusted for maternal age, education, race/ethnicity, asthma, allergies, smoking, birth year, parity, infant sex, gestational age, total gestational weight gain, and child's BMI. Risk ratios are presented relative to a reference of BMI=22 kg/m^2. Rug is presented along the x-axis of each graph to show distribution of data.

Figure B3.5: Figure S5: Average weight at each week of gestation among women

weighted that week
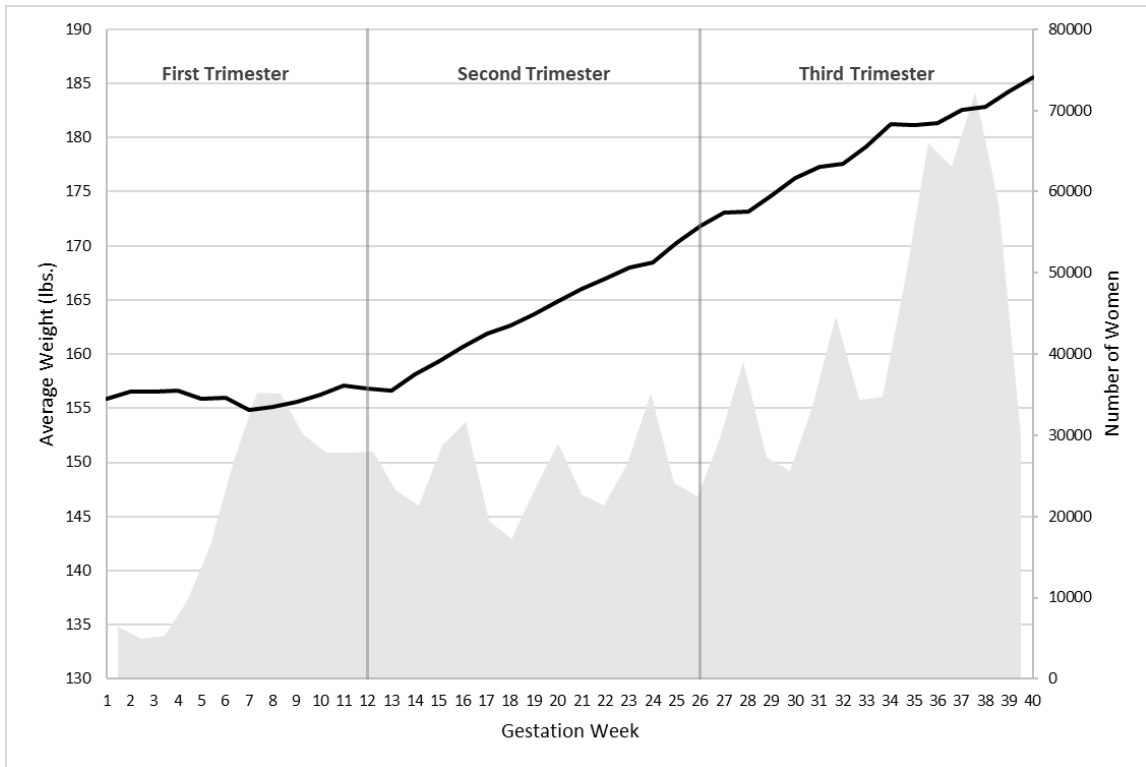
B4. DAGitty Code

The full *a priori* DAG was created using the following code on DAGitty (Textor J, Hardt J, Knüppel S. DAGitty: A Graphical Tool for Analyzing Causal Diagrams. *Epidemiology*. 2011;22(5):745. doi:10.1097/EDE.0b013e318225c2be):

```
dag {
"Birth Weight" [pos="0.187,1.674"]
"Caesarean Section" [pos="-0.450,1.081"]
"Child's 1st Year Antibiotics" [pos="1.078,1.747"]
"Child's BMI" [pos="0.567,-0.307"]
"Child's Sex" [pos="1.043,0.670"]
"Childhood Asthma" [outcome,pos="1.131,-0.108"]
"Gestational Age" [pos="-0.329,0.247"]
"Maternal Age" [pos="-1.817,-1.332"]
"Maternal Conditions (asthma/allergies)" [pos="0.720,-1.224"]
"Maternal Conditions (diabetes, hypertension)" [pos="-1.764,1.735"]
"Maternal Education" [pos="-1.471,-1.708"]
"NICU Admission" [pos="0.825,1.207"]
"Prenatal Antibiotics" [pos="-0.858,1.583"]
"Prepregnancy BMI" [exposure,pos="-2.000,-0.121"]
"Race/Ethnicity" [pos="-1.293,-1.224"]
"U-Genetics/Environment" [latent,pos="-1.975,-1.047"]
"U-SES" [latent,pos="-0.500,-1.739"]
Breastfeeding [pos="-1.960,1.142"]
GWG [pos="-1.221,0.056"]
Parity [pos="1.126,-1.726"]
Smoking [pos="0.227,-1.505"]
"Birth Weight" -> "Child's BMI"
"Birth Weight" -> "Childhood Asthma"
"Birth Weight" -> "NICU Admission" [pos="0.682,1.233"]
"Caesarean Section" -> "Child's 1st Year Antibiotics"
"Caesarean Section" -> "Childhood Asthma"
"Caesarean Section" -> "Gestational Age"
"Child's 1st Year Antibiotics" -> "Childhood Asthma" [pos="1.206,0.865"]
"Child's BMI" -> "Childhood Asthma"
"Child's Sex" -> "Birth Weight"
"Child's Sex" -> "Childhood Asthma"
"Child's Sex" -> "Gestational Age"
"Gestational Age" -> "Birth Weight"
"Gestational Age" -> "Childhood Asthma"
"Gestational Age" -> "NICU Admission"
"Maternal Age" -> "Caesarean Section"
"Maternal Age" -> "Prepregnancy BMI"
"Maternal Age" -> GWG
"Maternal Age" -> Parity
"Maternal Conditions (asthma/allergies)" -> "Childhood Asthma"
```

"Maternal Conditions (asthma/allergies)" -> "Prepregnancy BMI" [pos="0.302,-1.189"]

"Maternal Conditions (asthma/allergies)" -> Smoking

"Maternal Conditions (diabetes, hypertension)" -> "Birth Weight" [pos="-0.647,1.890"]

"Maternal Conditions (diabetes, hypertension)" -> "Caesarean Section" [pos="-1.101,1.561"]

"Maternal Conditions (diabetes, hypertension)" -> "Childhood Asthma"

"Maternal Conditions (diabetes, hypertension)" -> "Gestational Age" [pos="-0.610,0.381"]

"Maternal Education" -> "Birth Weight" [pos="-0.046,-0.203"]

"Maternal Education" -> "Child's BMI"

"Maternal Education" -> "Gestational Age" [pos="-0.600,-0.221"]

"Maternal Education" -> "Prepregnancy BMI"

"Maternal Education" -> Breastfeeding

"Maternal Education" -> Smoking [pos="-0.750,-1.285"]

"NICU Admission" -> "Child's 1st Year Antibiotics" [pos="0.978,1.505"]

"NICU Admission" -> "Childhood Asthma"

"Prenatal Antibiotics" -> "Childhood Asthma"

"Prenatal Antibiotics" -> GWG [pos="-1.113,1.038"]

"Prepregnancy BMI" -> "Birth Weight" [pos="-0.823,1.129"]

"Prepregnancy BMI" -> "Caesarean Section" [pos="-1.023,0.670"]

"Prepregnancy BMI" -> "Child's BMI" [pos="-0.318,-0.182"]

"Prepregnancy BMI" -> "Childhood Asthma"

"Prepregnancy BMI" -> "Gestational Age" [pos="-1.303,0.394"]

"Prepregnancy BMI" -> "Maternal Conditions (diabetes, hypertension)"

"Prepregnancy BMI" -> "Prenatal Antibiotics"

"Prepregnancy BMI" -> Breastfeeding

"Prepregnancy BMI" -> GWG

"Race/Ethnicity" -> "Birth Weight" [pos="-0.634,0.016"]

"Race/Ethnicity" -> "Child's BMI"

"Race/Ethnicity" -> "Maternal Education"

"Race/Ethnicity" -> "Prepregnancy BMI"

"U-Genetics/Environment" -> "Child's BMI"

"U-Genetics/Environment" -> "Prepregnancy BMI"

"U-SES" -> "Caesarean Section"

"U-SES" -> "Child's BMI" [pos="0.149,-0.843"]

"U-SES" -> "Childhood Asthma"

"U-SES" -> "Gestational Age"

"U-SES" -> "Maternal Education"

"U-SES" -> "Prepregnancy BMI"

"U-SES" -> Breastfeeding

Breastfeeding -> "Child's 1st Year Antibiotics"

Breastfeeding -> "Childhood Asthma"

GWG -> "Birth Weight" [pos="-0.808,1.497"]

GWG -> "Child's BMI" [pos="0.207,-0.130"]
GWG -> "Childhood Asthma"
GWG -> "Maternal Conditions (diabetes, hypertension)"
Parity -> "Caesarean Section"
Parity -> "Childhood Asthma"
Parity -> "Prepregnancy BMI"
Parity -> GWG
Smoking -> "Birth Weight"
Smoking -> "Childhood Asthma"
Smoking -> "Gestational Age"
Smoking -> "Maternal Conditions (diabetes, hypertension)"
Smoking -> "Prepregnancy BMI"
Smoking -> GWG
}

B5. Additional Information

B5.1 Covariate definitions

Maternal characteristics included age (<25, 25-29, 30-34, 35-39, ≥40 years), education (<12, 12-15, ≥16 years), self-identified race and ethnicity (White, Black, Asian/Pacific Islander, Hispanic, other/missing), asthma (active during this pregnancy, past, none; determined using diagnoses reported on medical intake forms, and medication dispensing), allergies (yes/no; including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the EMR), smoking during this pregnancy (yes/no), prepregnancy diabetes (yes/no), gestational diabetes (yes/no), chronic hypertension (yes/no), gestational hypertension (yes/no), breastfeeding (never, <3, 3-6, >6 months; collected prospectively on repeated surveys during child well-visits), prenatal antibiotics (yes/no), cesarean delivery (yes/no), and total GWG (calculated as delivery weight minus prepregnancy weight; implausible values [GWG <-40 lbs. and GWG >100 lbs.] were set to missing). Child characteristics were birth year (2005-2014), gestational age (<31, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, ≥41 weeks), infant sex (male/female), birth weight (<2500, 2500-4000, >4000 grams), parity (first, second, or third+ born), neonatal intensive care unit (NICU) admission (yes/no), first year antibiotics (yes/no), and child BMI percentiles (<5th [underweight], 5th-85th [normal], 85th-95th[overweight], >95th [obese]); calculated using height and weight measurements within 6 months of previous birthday).

B5.2 Gestational weight gain operationalizations

In our final models, continuous total GWG (calculated as delivery weight minus prepregnancy weight) was modeled flexibly using a cubic spline with knots on percentiles. In the literature, GWG is inconsistently operationalized and there is debate on which method is most informative.[1] Sensitivity analyses were conducted operationalizing GWG differently. These included (1) continuous total GWG, (2) total GWG categories in 10 lbs. increments, (3) total GWG categories defined by Institute of Medicine (IOM) for

each BMI category[2] (inadequate, adequate, excessive), (4) trimester specific total GWG, and (5) trimester specific continuous total GWG modeled with cubic splines.

B5.3 Additional results

Figure S2 shows models excluding covariates that could be considered mediators, specifically: GWG, gestational age, and child's BMI. The resulting risk ratios (RRs) without adjustment for GWG, gestational age, and child's BMI are as follows (labeled "Remove GWG, Child BMI, Gestational Age" in Figure S2):

RRs (relative to Normal BMI) in the age 4 cohort were:
- 0.92 (95% CI: 0.75, 1.11) for underweight,
- 1.09 (95% CI: 1.02, 1.16) for overweight,
- 1.14 (95% CI: 1.05, 1.24) for obese class 1, and
- 1.19 (95% CI: 1.09, 1.31) for obese class 2/3

RRs (relative to Normal BMI) in the age 6 cohort were:
- 0.95 (95% CI: 0.78, 1.16) for underweight,
- 1.11 (95% CI: 1.03, 1.18) for overweight,
- 1.18 (95% CI: 1.08, 1.29) for obese class 1, and
- 1.23 (95% CI: 1.12, 1.36) for obese class 2/3

RRs (relative to Normal BMI) in the age 8 cohort were:
- 0.96 (95% CI: 0.74, 1.25) for underweight,
- 1.07 (95% CI: 0.97, 1.17) for overweight,
- 1.09 (95% CI: 0.97, 1.23) for obese class 1, and
- 1.19 (95% CI: 1.05, 1.36) for obese class 2/3

B5.4 Additional discussion

Breastfeeding, prenatal antibiotics, cesarean section, birth weight, NICU admission, and child's first year antibiotics did not affect model estimates and were not included in final adjusted models. These covariates are typically included in other studies (in part or in combination when the information is available). Although these were not influential covariates in our analysis, each has been associated with prepregnancy BMI and child's asthma, although whether these associations represent causal, indirect, or backdoor confounding pathways is unclear. Previous studies also commonly adjusted for maternal comorbidities such as prepregnancy diabetes, gestational diabetes, chronic hypertension, and gestational hypertension. Though there is inconsistent differentiation between chronic and gestational timing of these conditions. There is strong evidence linking prepregnancy BMI with all these conditions,[3–5] but evidence linking these conditions to child's asthma is weak and inconsistent.[6–9] Ultimately, these covariates did not affect model estimates and were left out of final adjusted models.

B5.5 References
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Appendix C: Supplemental Material for Gestational Weight Gain and Childhood

Asthma Risk

Covariate Definitions

      Covariates were obtained from the mother's and child's electronic medical records. Maternal characteristics included age (<25, 25-29, 30-34, 35-39, ≥40 years), education (<12, 12-15, ≥16 years), self-identified race and ethnicity (White, Black, Asian/Pacific Islander, Hispanic, other/missing), asthma (active during this pregnancy, past, none; determined using diagnoses reported on medical intake forms, and medication dispensing), allergies (yes/no; including diagnoses for allergic rhinitis, atopic dermatitis, food allergies, or other allergies at any time in the EMR), smoking during this pregnancy (yes/no), prepregnancy diabetes (yes/no), gestational diabetes (yes/no), chronic hypertension (yes/no), gestational hypertension (yes/no), breastfeeding (never, <3, 3-6, >6 months; collected prospectively on repeated surveys during child well-visits), prenatal antibiotics (yes/no), cesarean delivery (yes/no). Child characteristics were birth year (2005-2014), infant sex (male/female), birth weight (<2500, 2500-4000, >4000 grams), parity (first, second, or third+ born), neonatal intensive care unit (NICU) admission (yes/no), first year antibiotics (yes/no), and child BMI percentiles (<5th [underweight], 5th-85th [normal], 85th-95th[overweight], >95th [obese]); calculated using height and weight measurements within 6 months of previous birthday).

Figure C1: Figure S1: Directed acyclic graph (DAG) of gestational weight gain (GWG) and child's asthma showing confounding and mediating pathways
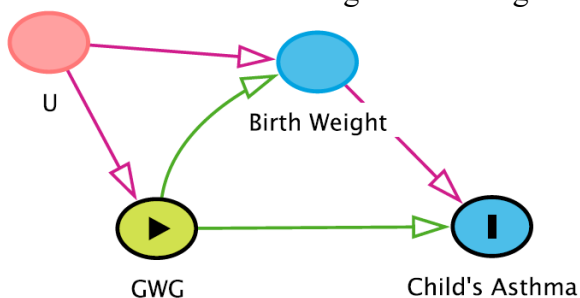
Abbreviations: GWG – gestational weight gain
Legend:
Exposure = GWG
Outcome = child's asthma
Green arrow = causal pathway
Pink arrow = biasing pathway
Notes: The above figure shows an example of how some covariates could be considered both intermediates (on the pathway) and/or confounders (though backdoor pathways) between GWG and child's asthma. GWG and birthweight are likely affected by unmeasured common causes such as environmental factors (U). Though birth weight could also be on the causal pathway between GWG and child's asthma.

Secondary Asthma Definition

      This asthma outcome definition only required one controller medication dispensing in the child's electronic medical record history and either an asthma diagnosis

or one controller prescription medication dispensing in the past twelve months of each relevant follow-up age (age 4 or age 6). All children who met the criteria for the primary definition also met the criteria for the secondary definition.

Parametric G-Formula

      The g-computation algorithm formula (g-formula) is a method used to estimate the effect of time-varying exposures while accounting for time-dependent confounding.[1] Through causal identification assumptions, the g-formula links to the observed data representing a generalization of standardization of time-varying exposures and confounders in a longitudinal study setting. These relationships among the observed data can be parametrically modeled, thus denoted as the parametric g-formula. General assumptions for implementing the parametric g-formula include no unmeasured confounding (at all time points), no measurement error, and no model misspecification.[1] Here we describe the algorithms and models used to implement the parametric g-formula among the age 4 follow-up cohort, which can be applied analogously for the age 6 follow-up cohort.

Algorithm

The risk of childhood asthma under the natural course (no intervention on GWG) standardized for time-varying exposures and confounding is given in Equation 1. To estimate this, we fit parametric models for each of the component variables: remaining pregnant, amount of weight gain, and asthma diagnosis.

(1) The probability of remaining pregnant each week was modeled using logistic regression controlled for fixed covariates *(*maternal age, education, race/ethnicity, asthma, allergies, smoking during pregnancy, birth year, infant sex, and parity), cumulative weight gained up to the previous week, and cumulative number of weeks pregnant up to the previous week. Specifically, we fit the model shown in Equation 2.

(2) The weekly density of weight gained was modeled using linear regression controlling for fixed covariates (maternal age, education, race/ethnicity, asthma, allergies, smoking during pregnancy, birth year, infant sex, and parity), cumulative weight gained up to the previous week, and cumulative number of weeks pregnant up to the previous week. See Equation 3 for the specific model.

(1) The probability of childhood asthma after pregnancy follow-up ended was modeled using logistic regression conditional on fixed covariates (maternal age, education, race/ethnicity, asthma, allergies, smoking during pregnancy, birth year, infant sex, and parity), cumulative weight gained up to the week before birth, and cumulative number of weeks pregnant up to the week before birth. The outcome model is shown in Equation 4.

      To estimate the risk of childhood asthma under the natural course, we drew a large Monte Carlo sample of mother-child pairs (N=50,000) with replacement from the original data stratifying by prepregnancy BMI categories (normal, overweight, obese class 1 and obese class 2/3). In the first week (i.e., at the first timepoint) fixed covariates (maternal age, education, race/ethnicity, asthma, allergies, smoking during pregnancy, birth year,

infant sex, and parity) are set to observed values, all mothers are considered pregnant, and no weight gain has occurred. Then for each sampled mother-child pair, we predicted remaining pregnant, and weight gained in each week thereafter until birth (i.e., predicted to no longer pregnant). If a woman was predicted to give birth that week, weekly weight gain would no longer be predicted for her, demonstrating that she can no longer gain weight related to pregnancy. Childhood asthma outcome was predicted for the final week only, indicating outcome was measured after pregnancy follow-up time ended. This pseudo-cohort was created with no censoring due to dropout. Using this pseudo-cohort, we estimated the risk of childhood asthma averaged over this simulated population, summed over all covariate histories, and weighted by the frequency of specific covariate histories. This standardized risk can be viewed as the weighted average of the risks of asthma conditional on the observed confounder history, including time-dependent confounding. We then operationalized GWG the same way as the main paper analysis for comparison.

Models

Let i index the 100,929 (n) mother-child pairs in the age 4 cohort. Gestational age in weeks was indexed by k=0 to 40 (K); with k=0 corresponding to conception when all mother-child pairs entered the cohort. For mother-child pair i, C_i represents the time-fixed 'baseline' covariates including maternal age, education, race/ethnicity, asthma, allergies, smoking during pregnancy, birth year, infant sex, and parity. Although some of these variables were not measured at k=0 ('baseline') they are included in this list of time-fixed covariates because they were only measured once during follow-up and are block important confounding paths. P_{ik} represents pregnancy status for mother-child pair i during week k, with P=1 being remaining pregnant and P=0 being no longer pregnant (i.e., born that week). All mother-child pairs began follow-up pregnant (i.e., when k=0 then P=1). Let G_{ik} represent the weight gained for mother-child pair i during week k. Mother-child pairs were assumed to gain weight if they remained pregnant (i.e., when P_{ik}=1 then $G_{ik} \neq 0$) and to not gain weight (related to pregnancy) after birth (i.e., when P_{ik}=0 then G_{ik}=0). Let Y_{ik}=1 represent childhood asthma diagnosis during week $k+t$, where t is the number of weeks after birth until the child was diagnosed with asthma (e.g., when age=4 then t=208); indicating that the childhood asthma outcome was measured after pregnancy follow-up time ended. Overbars indicate histories for time-varying covariates (e.g., $\bar{P}_k$ = {Pk, Pk+1, …PK}). The temporal ordering of component variables for each mother-child pair each gestational week were as follows: remaining pregnant, amount of weight gained, and asthma diagnosis (only for last time point). In all following equations, the subscript i (indexing mother-child pairs) has been suppressed.

Equation 1: natural course

$$I(k) = \sum_{k=0}^{40} \sum_{v} \sum_{\bar{p}_k} \sum_{\bar{g}_k} \Bigg\{ P(Y_K = 1 | C = c, \bar{P}_k = \bar{p}_k, \bar{G}_k = \bar{g}_k,)$$

$$* \prod_{m=0}^{k} [f(C = c) * P(P_m = 1 | C = c, \bar{P}_{m-1} = \bar{p}_{m-1}, \bar{G}_{m-1} = \bar{g}_{m-1},)$$

$$* f(G_m = g_m | C = c, \bar{P}_{m-1} = \bar{p}_{m-1}, \bar{G}_{m-1} = \bar{g}_{m-1},)] \Bigg\}$$

Equation 2: remaining pregnant

$logit[Pr(P_k = 1 | \bar{P}_{k-1} = 1, C = c, \bar{G}_{k-1} = \bar{g}_{k-1})] = \alpha_0 + \alpha_1'(c) + \alpha_2'(g_{k-1})$

Where $\alpha_1'(c)$ is a vector of parameter coefficients for all fixed covariates (listed above) and α_2' is a vector of parameter coefficients for the terms of a function of exposure history $(\bar{g}_{k-1})$.

Equation 3: weight gained

$E(G_k | \bar{P}_{k-1} = 1, C = c, \bar{G}_{k-1} = \bar{g}_{k-1}) = \beta_0 + \beta_1'(c) + \beta_2'(\bar{g}_{k-1})$

Where $\beta_1'(c)$ is a vector of parameter coefficients for all fixed covariates (listed above) and β_2' is a vector of parameter coefficients for the terms of a function of exposure history $(\bar{g}_{k-1})$.

Equation 4: childhood asthma outcome

$logit[Pr(Y_{k+t} = 1 | C = c, \bar{G}_k = \bar{g}_k, \bar{P}_k = \bar{p}_k)] = \gamma_0 + \gamma_1'(c) + \gamma_2'(\bar{g}_{k-1}) + \gamma_3'(\bar{p}_{k-1})$

Where γ_1' is a vector of parameter coefficients for all fixed covariates (c), γ_2' is a vector of parameter coefficients for the terms of a function of weight gain history $(\bar{g}_{k-1})$, and γ_3' is a vector of parameter coefficients for the terms of a function of pregnancy history $(\bar{p}_{k-1})$.

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