

Maternal Obesity in Pregnancy, Gestational Weight Gain, and Risk of Childhood Asthma

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KEY WORDS

childhood asthma, asthma risk factors, maternal obesity, gestational weight gain, meta-analysis

ABBREVIATIONS

CI—confidence interval

CINAHL—Cumulative Index to Nursing and Allied Health Literature

GWG—gestational weight gain

MOP—maternal obesity in pregnancy

OR—odds ratio

STROBE—Strengthening the Reporting of Observational Studies in Epidemiology

TNF- α —tumor necrosis factor α

Dr Forno formulated the idea for the study and participated in the study design, literature searches, study selection, data abstraction, analysis, and interpretation and the writing of the manuscript; Dr Young participated in the study design, literature searches, study selection, data abstraction, analysis, and interpretation and the writing of the manuscript; Dr Kumar participated in the data interpretation and the writing of the manuscript; Dr Simhan contributed to the data analysis and interpretation and participated in the writing of the manuscript; Dr Celedón contributed to the data analysis and interpretation and participated in the writing of the manuscript; and all authors approved the final manuscript as submitted. Dr Forno and Dr Young contributed equally to this manuscript.

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abstract



BACKGROUND AND OBJECTIVE: Environmental or lifestyle exposures in utero may influence the development of childhood asthma. In this meta-analysis, we aimed to assess whether maternal obesity in pregnancy (MOP) or increased maternal gestational weight gain (GWG) increased the risk of asthma in offspring.

METHODS: We included all observational studies published until October 2013 in PubMed, Embase, CINAHL, Scopus, The Cochrane Database, and Ovid. Random effects models with inverse variance weights were used to calculate pooled risk estimates.

RESULTS: Fourteen studies were included ($N = 108\,321$ mother-child pairs). Twelve studies reported maternal obesity, and 5 reported GWG. Age of children was 14 months to 16 years. MOP was associated with higher odds of asthma or wheeze ever (OR = 1.31; 95% confidence interval [CI], 1.16–1.49) or current (OR = 1.21; 95% CI, 1.07–1.37); each 1-kg/m² increase in maternal BMI was associated with a 2% to 3% increase in the odds of childhood asthma. High GWG was associated with higher odds of asthma or wheeze ever (OR = 1.16; 95% CI, 1.001–1.34). Maternal underweight and low GWG were not associated with childhood asthma or wheeze. Meta-regression showed a negative association of borderline significance for maternal asthma history ($P = .07$). The significant heterogeneity among existing studies indicates a need for standardized approaches to future studies on the topic.

CONCLUSIONS: MOP and high GWG are associated with an elevated risk of childhood asthma; this finding may be particularly significant for mothers without asthma history. Prospective randomized trials of maternal weight management are needed. *Pediatrics* 2014;134:e535–e546

Obesity is a major public health problem, affecting >35% of the adult population in the United States¹ and complicating up to 20% of pregnancies in this country.¹ Maternal obesity is defined as a BMI ≥ 30 kg/m², and maternal overweight is defined as a BMI between 25 and 29.9 kg/m².² Maternal obesity is further stratified into classes: class I (BMI 30–34.9), class II (BMI 35–39.9), and class III (BMI ≥ 40).³ Maternal obesity in pregnancy (MOP) has been associated with adverse pregnancy outcomes, including hypertensive disorders of pregnancy, gestational diabetes, and need for operative delivery.^{4,5} Maternal obesity also has a significant impact on fetal development, the neonatal period, and overall childhood development. It has been associated with an elevated incidence of fetal neural tube defects such as spina bifida and anencephaly.^{6,7} Moreover, higher gestational weight gain (GWG) increases the risk of small size for gestational age and of iatrogenic preterm birth.⁸

In recent years, there has been growing interest on how in utero exposures predispose infants to diseases throughout the life span. For example, British epidemiologist David Barker⁹ reported that people with a history of low birth weight were at elevated risk of coronary artery disease later in life and, in what came to be known as the Barker hypothesis,¹⁰ theorized that the origins of complex diseases may stem from intrauterine exposures. Thus, MOP may significantly affect life ex utero for years to come. Given the substantial impact of maternal obesity on not only maternal but also fetal and neonatal outcomes, in 2009 the Institute of Medicine³ recommended that obese women limit their GWG to between 11 and 20 pounds.

Asthma, a complex disease that affects ~7 million children in the United States,¹¹ can result from interactions

between hereditary and environmental factors^{12,13} beginning in utero. For example, maternal smoking during pregnancy increases the risk of asthma in offspring¹⁴ and may hinder age-dependent improvement in airway hyperreactivity among children with asthma.¹⁵

Along these lines, there is growing evidence that MOP or high GWG is associated with elevated risk of asthma or wheeze (a symptom of asthma) in offspring.^{16–18} It is thought that in utero exposure to different dietary patterns or to the proinflammatory milieu of obesity may affect fetal immune or pulmonary development, thus leading to asthma.¹⁷ Therefore, the aims of this meta-analysis were to quantitatively estimate the effect of MOP or GWG on childhood asthma or wheeze, to generate a pooled analysis of studies available in the literature, and to explore factors that may modify the effect of MOP on childhood asthma.

METHODS

We prospectively registered the protocol for this meta-analysis in PROSPERO on September 5, 2013: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005490.

Sources and Study Selection

We searched PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, the Cochrane Database, and Ovid for observational studies evaluating the association between MOP or GWG and asthma or wheeze in childhood, published up to October 2013. Initial inclusion criteria were as follows:

- Study design: Observational studies published in English (or in languages other than English when able to translate into English or when enough information was available in an English abstract for use in the data analysis).

- Population: Children in whom outcomes were measured between birth and <18 years of age. Mothers in whom BMI at the beginning of pregnancy was ascertained directly or by report at some point during pregnancy or whose GWG was ascertained directly or by report in the third trimester of pregnancy.
- Outcomes: Wheeze or asthma during childhood, determined by report, doctor's diagnosis, medical record review, or evaluation by the study team. When >1 time point for such assessment existed, only the latest point available was included.

Two authors (E.F. and O.M.Y.) independently retrieved and screened all studies according to these predetermined selection criteria. In addition, we manually screened references in the selected articles for additional relevant studies. Initial selection was based on title and abstract screening, and final selection was performed using full texts. Exclusion criteria were ineligible study design (eg, interventional study for management of MOP or GWG or for prevention of childhood asthma or wheeze), ineligible population (eg, adults), ineligible outcomes (eg, other than childhood asthma or wheeze), and insufficient information in English to determine inclusion criteria and abstract risk estimates. Differences of opinion for inclusion were resolved by discussion.

Data Extraction and Quality Assessment

Using a uniform data extraction form, 2 of the authors (E.F. and O.M.Y.) independently extracted from full-text articles all data on references (first author, year of publication), number of participants, timing of MOP or GWG determination (eg, gestational age at which “final” maternal weight was

ascertained), BMI or GWG (means or categories) as reported by the original studies, outcome definitions, ages at which outcomes were measured, total number of participants, number of participants with and without the outcomes when available, odds ratios (ORs) or risk ratios with their corresponding confidence intervals (CIs), and relevant covariates as reported in the original studies (eg, mean maternal age, race, smoking exposure during pregnancy or childhood). Disagreements on data extraction between the 2 authors were resolved through mutual discussion and, if needed, consultation with a third author (J.C.C.). Agreement between the reviewers on study selection was determined by using the Cohen k statistic (κ). The quality of reporting in the included studies was assessed by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist.¹⁹ Studies were graded as A (>85% of STROBE criteria fulfilled), B (50–85%), or C (<50%).

Analysis

Data collected were pooled to generate summary estimates; each study was weighed by its inverse effect size variant. To evaluate the association of MOP or GWG, we calculated ORs for the development of childhood asthma or wheeze. Many studies provided different categories for MOP and GWG; therefore, when possible we contacted the corresponding authors of the original studies to provide us with estimates for BMI and GWG (in kilograms) as continuous variables. We tested for heterogeneity in results across studies by using a Cochran Q statistic; the I^2 statistic was used to quantify the extent of true heterogeneity. ORs and their CIs were calculated by using random effects models. Egger tests were used to assess for potential publication bias. Subgroup analyses by outcome definition and age group and

meta-regression analyses were conducted to explore potential sources of heterogeneity and assess effect modification by different covariates such as maternal age, race, and smoking exposure. All analyses were performed in Stata version 12 (Stata Corp, College Station, TX), and a P of .05 was considered statistically significant.

RESULTS

A total of 474 studies were identified (Fig 1): 398 from PubMed, 31 from Embase, 28 from Scopus, 7 from Cumulative Index to Nursing and Allied Health Literature, 1 from the Cochrane Database, and 9 from Ovid; no additional references were identified from reviewing references in relevant articles. Of these, 14 studies with a total of 108 321 mother–child pairs were included in the meta-analysis^{16–18,20–30} (Table 1). There was complete agree-

ment on 469 of 474 articles after title and abstract screening (interreader agreement $\kappa = .90$) and on 40 of 42 articles after full-text screening ($\kappa = .89$).

Characteristics of Included Studies

Included studies were published between March 1996 and October 2013. Twelve studies reported maternal BMI (continuous or categorical) closely before or at the beginning of pregnancy^{16–18,20–23,25–27,29,30} and were included in the analysis of MOP; 5 studies were included in the analysis of GWG.^{20,21,23,24,28} Although many studies categorized MOP and GWG in different ways, response from the authors of the original studies was very positive, and the majority of them provided us with estimates for continuous BMI^{18,20–23,27} and GWG (in kilograms)^{20,21} (or kindly responded that continuous data were

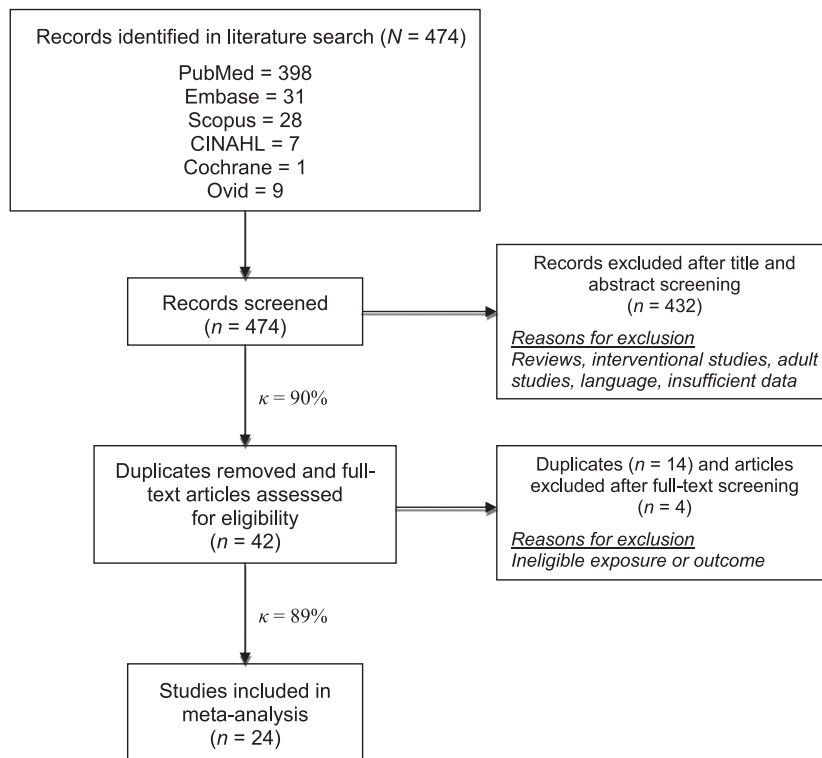


FIGURE 1

Flowchart of study selection. κ indicates Cohen's κ agreement coefficient (1.0 = perfect agreement). (Flowchart adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for systematic reviews and meta-analyses.⁵⁰)

TABLE 1 Characteristics of Studies Included in the Metaanalysis

Reference	N	Age of Children at Outcome	City or Country	Ascertainment of Exposure; Outcome	Risk Estimates as Originally Reported	Comments	Quality Score ^a
Caudri et al 2013 ¹⁶	3963	8 y	Netherlands	Self-report; self-report	Persistent wheeze: Continuous prepregnancy BMI, OR = 1.26 (CI, 1.01–1.57).	Adjusted for gender, parental allergy, smoke exposure, breastfeeding, day care, pregnancy duration, older siblings, birth wt, maternal age, study region, parental education, and maternal asthma.	A
Guerra et al 2013 ¹⁷	1107	14 mo	Spain	Self-report	Frequent wheeze: Continuous BMI, OR = 1.08 (CI, 1.01–1.15). BMI categories: BMI < 18.5, OR = 1.7 (CI, 0.3–8.3); BMI 25–30, OR = 1.0 (CI, 0.4–2.6); BMI > 30, OR = 4.2 (CI, 1.5–11.3).	Adjusted for maternal socioeconomic status, child's gender and wt for length, type of delivery, preterm birth, birth wt, day care, breastfeeding, maternal age, parity, and smoking, and parental asthma.	A
Håberg et al 2009 ¹⁸	32 281	18 mo	Norway	Self-report; self-report	Wheeze: BMI categories: BMI 25–30, RD = 0.4 (CI, –1.1, 1.8); BMI > 30, RD = 3.3 (CI, 1.2, 5.3).	Adjusted for maternal age, parity, education, income, asthma, and smoking in pregnancy, parental smoking after birth, breastfeeding, day care, child's gender, low birth wt, preterm birth, and cesarean section. Continuous data obtained directly from the author.	A
Halonen et al 2013 ²⁰	261	9 y	United States (Tucson, AZ)	Medical records; measured	Asthma: Prepregnancy BMI tertiles: Middle tertile OR = 0.5 (CI, 0.2–1.3); high OR = 0.4 (CI, 0.2–1.1). GWG categories: High GWG, OR = 3.4 (CI, 1.6–7.2).	Adjusted for maternal age, ethnicity, and parity, parental smoking, and child's gender. Continuous data obtained directly from the author.	A
Harpsee et al 2013 ²¹	38 874	7 y	Denmark	Self-report; self-report	Asthma ever: BMI categories: BMI < 18.5, OR = 1.03 (CI, 0.88–1.22); BMI 25–30, OR = 1.22 (CI, 1.12–1.33); BMI 30–35, OR = 1.56 (CI, 1.36–1.79); BMI > 35, OR = 1.55 (CI, 1.23–1.95). GWG categories: < 5 kg, OR = 1.17 (CI, 0.94–1.45); 5–9 kg, OR = 1.02 (CI, 0.91–1.15); 16–19 kg, OR = 0.97 (CI, 0.89–1.06); 20–24 kg, OR = 1.15 (CI, 1.05–1.27); > 25 kg, OR = 1.19 (CI, 1.04–1.35). Current asthma: BMI categories: BMI < 18.5, OR = 1.07 (CI, 0.85–1.34); BMI 25–30, OR = 1.24 (CI, 1.10–1.38); BMI 30–35, OR = 1.58 (CI, 1.32–1.90); BMI > 35, OR = 1.48 (CI, 1.08–2.04). GWG categories: < 5 kg, OR = 0.84 (CI, 0.60–1.17); 5–9 kg, OR = 1.11 (CI, 0.96–1.29); 16–19 kg, OR = 0.90 (CI, 0.80–1.02); 20–24 kg, OR = 1.15 (CI, 1.01–1.31); > 25 kg, OR = 1.23 (CI, 1.03–1.46).	Adjusted for maternal age, race, socioeconomic status, smoking during pregnancy, atopy, day care use, atopy, cesarean delivery, child gender, and number of siblings. Continuous data obtained directly from the author.	A

TABLE 1 Continued

Reference	N	Age of Children at Outcome	City or Country	Ascertainment of Exposure; Outcome	Risk Estimates as Originally Reported	Comments	Quality Score ^a
Kumar et al 2010 ²²	1191	3 y	United States (Boston, MA)	Self-report	Recurrent wheezing: BMI categories: BMI 25–30, OR = 1.58 (CI, 0.75–3.30); BMI >30, OR = 3.51 (CI, 1.68–7.32).	Adjusted for maternal age, race, education, atopy, child's gender, premature delivery, smoking during pregnancy and at home, fetal growth retardation, and large size for gestational age. Continuous data obtained directly from the author.	A
Leermakers et al 2013 ²³	4656	4 y	Netherlands	Self-report; measured	Current wheeze: No family history: Continuous BMI, OR = 1.02 (CI, 0.95–1.08). Categories: BMI <20, OR = 0.93 (CI, 0.79–1.09); BMI 25–30, OR = 1.09 (CI, 0.95–1.26); BMI >30, OR = 0.93 (CI, 0.73–1.19). Continuous GWG OR = 1.10 (CI, 1.03–1.16). Positive family history: Continuous BMI, OR = 1.06 (CI, 0.98–1.43). Categories: BMI <20, OR = 1.19 (CI, 0.98–1.43); BMI 25–30, OR = 0.95 (CI, 0.80–1.14); BMI >30, OR = 1.41 (CI, 1.06–1.87). Continuous GWG, OR = 1.09 (CI, 1.01–1.17).	Study included 2 subgroups. Adjusted for maternal age, parity, ethnicity, education, smoking during pregnancy, pets, gestational complications, gestational age at measurement, child's gender, gestational age at birth, birth wt, breastfeeding, day care, and child's height and wt at follow-up. Continuous data obtained directly from the author.	A
Oliveti et al 1996 ²⁴	262	4–9 y	United States (Cleveland, OH)	Medical records	Asthma: GWG category (<9 kg): OR = 3.42 (CI, 1.72–6.79).	Adjusted for maternal asthma history, bronchiolitis, maternal smoking, lack of prenatal care, use of oxygen at birth, prematurity, low birth wt <2500 g, and 5-min Apgar score.	B
Patel et al 2012 ²⁵	6945	15–16 y	Northern Finland	Medical records	Wheeze ever: BMI categories for wheeze (ever) or asthma (ever): BMI <18.5, OR = 0.80 (CI, 0.58–1.09); BMI 25–30, OR = 1.18 (CI, 0.95–1.47); BMI <30, OR = 0.99 (CI, 0.66–1.48). Continuous BMI, OR = 1.028 (CI, 1.005–1.051). Current wheeze: BMI categories for wheeze (current) or asthma (current): BMI <18.5, OR = 0.87 (CI, 0.57–1.04); BMI 25–30, OR = 1.13 (CI, 0.85–1.30); BMI <30, OR = 1.54 (CI, 0.97–2.44). Continuous BMI, OR = 1.047 (CI, 1.019–1.077).	Adjusted for socioeconomic status, marital status, maternal education, maternal asthma, birth wt, parental smoking during gestation, and adolescent BMI at age 15 y.	A
Pike et al 2013 ²⁶	940	6 y	United Kingdom	Measured	Continuous BMI: Asthma ever: OR = 1.06 (CI, 0.91–1.24). Current asthma: OR = 1.10 (CI, 0.92–1.32). Wheeze ever: OR = 1.08 (CI, 1.02–1.13). Current wheeze: OR = 1.02 (CI, 0.87–1.20).	Adjusted for maternal education, asthma, smoking in pregnancy, parity, child's gender, birth wt, breastfeeding, and other outcome-specific covariates.	A

TABLE 1 Continued

Reference	N	Age of Children at Outcome	City or Country	Ascertainment of Exposure; Outcome	Risk Estimates as Originally Reported	Comments	Quality Score ^a
Reichman and Nepomnyaschy 2008 ²⁷	1971	3 y	United States	Medical records	Asthma ever: BMI >30, OR = 1.34 (CI, 1.03–1.76).	Adjusted for maternal age, education, income, race, smoking during pregnancy, parental smoking, preterm delivery, child age, gender, and BMI. Continuous data obtained directly from the author.	A
Rusconi et al 2007 ²⁸	15 609	6–7 y	Italy	Self-report; self-report	Persistent wheezing: GWG <9 kg, OR = 1.08 (CI, 0.84–1.39). GWG >15 kg, OR = 1.20 (CI, 0.98–1.48).	Adjusted for maternal age, education, smoking, study center, parental asthma or atopy, child gender, low birth wt, siblings, socioeconomic status, season, and person who completed the questionnaire. Author responded but continuous data not available.	B
Schoffens et al 2010 ²⁹	3963	8 y	Netherlands	Self-report	Continuous BMI, no family history: Asthma: OR = 0.98 (CI, 0.94–1.02). Wheeze: OR = 1.01 (CI, 0.69–1.07). Continuous BMI, positive family history: Asthma: OR = 1.05 (CI, 1.01–1.10). Wheeze: OR = 1.06 (CI, 1.01–1.12). Repeated wheeze: BMI >30, OR = 2.65 (CI, 1.01–6.95).	Adjusted for maternal education, smoking, asthma, breastfeeding, mode of delivery, birth wt, and child's BMI at 8 y of age.	A
Wright et al 2013 ³⁰	261	2 y	United States (Boston, MA)	Measured	Adjusted for maternal age, race, education, prenatal smoking, atopy, child's gender, birth wt adjusted for gestational age, and serum cortisol levels (afternoon slope). Continuous data unavailable.	Adjusted for maternal age, race, education, prenatal smoking, atopy, child's gender, birth wt adjusted for gestational age, and serum cortisol levels (afternoon slope). Continuous data unavailable.	A

Table shows characteristics of individual studies, including outcome, obesity categories, and ORs as defined and reported in the original manuscript, as well as reported covariates used in their adjusted models.

^a Quality of reporting assessment based on STROBE statement criteria.¹⁹

not available²⁸). For prepregnancy BMI, 7 studies used maternal self-report of height or weight,^{16–18,21–23,29} and 5 used medical records or directly measured both.^{20,25–27,30} For GWG, 4 studies used the difference between weight in the third trimester and that in the first trimester,^{20,23,24,28} and 1 used maternal report of weight gain.²¹ Outcomes reported varied and included wheezing (ever, current, transient, or persistent) and asthma (ever or current); 12 studies used self-report (of which 3 studies specified “report of physician-diagnosed asthma”^{20,21,27}), and 2 studies reported using physician diagnosis or medical record review.^{22,24} For comparability purposes, we grouped (when possible) the outcomes into 2 broader categories: “asthma/wheeze ever”^{17,18,20–22,25–30} and “current asthma/wheeze.”^{21,23–26,29}

Maternal Obesity During Pregnancy

Table 1 shows the original studies with the MOP as reported (categorical or continuous) and the reported outcomes. Given heterogeneity of outcomes, we grouped them into “asthma/wheeze ever” and “current asthma/wheeze.” Figure 2 shows the pooled analysis by BMI categories. Compared with children from mothers of normal weight, those whose mothers were obese had higher odds of asthma or wheeze ever (OR = 1.49; 95% CI, 1.22–1.83; *P* < .001) and current asthma or wheeze (OR = 1.36; 95% CI, 1.08–1.68; *P* = .008). Maternal overweight showed nonsignificant trends for asthma or wheeze ever (OR = 1.13; 95% CI, 0.99–1.29; *P* = .06) and current asthma or wheeze (OR = 1.11; 95% CI, 0.98–1.25; *P* = .09). When analyzed together, maternal overweight or obese (BMI >25) led to higher odds of asthma or wheeze ever (OR = 1.31; 95% CI, 1.16–1.49; *P* < .001) and current asthma or wheeze (OR = 1.21; 95% CI, 1.07–1.37; *P* = .003) (Supplemental Figure 6). Maternal underweight

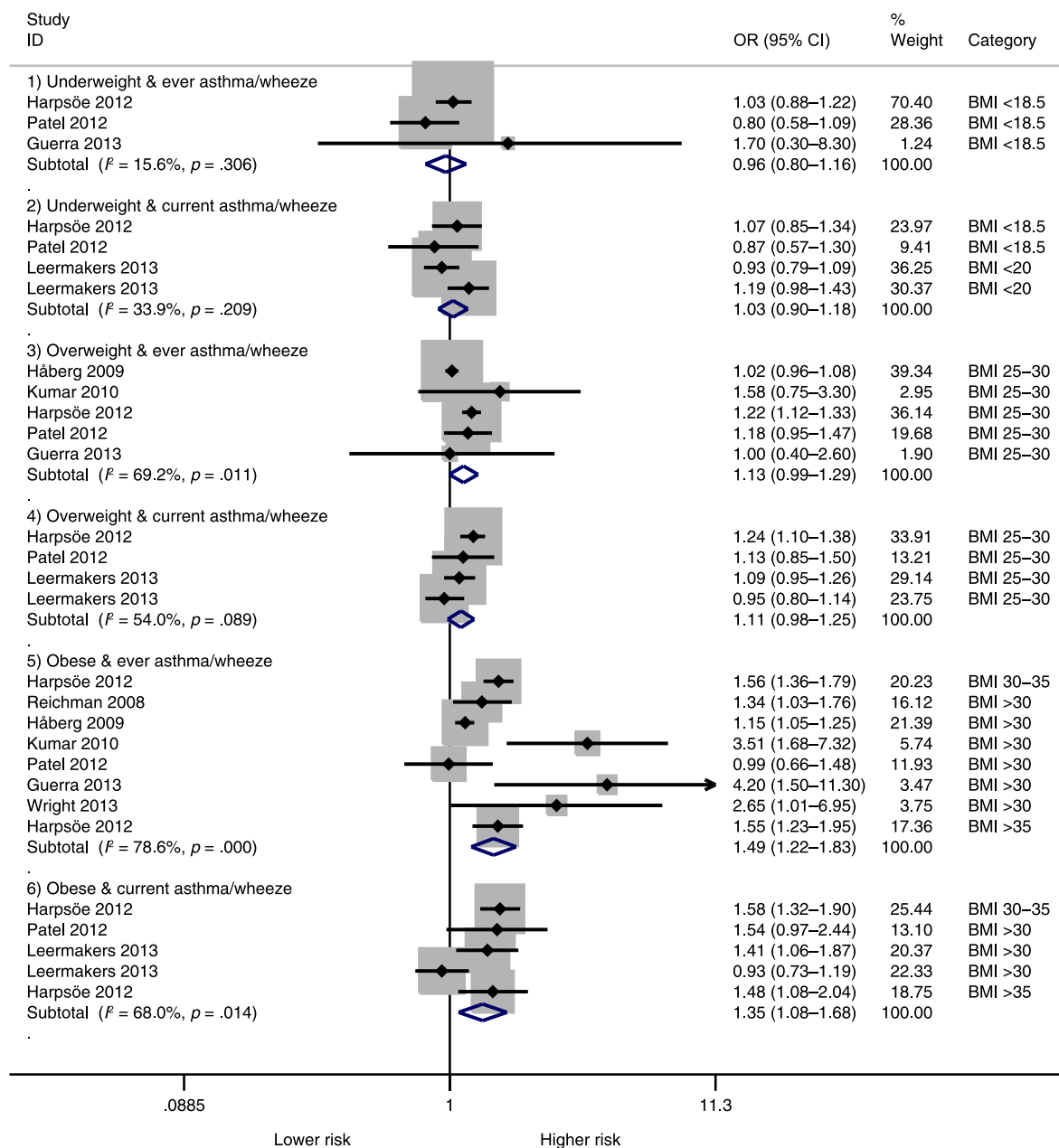


FIGURE 2

Pooled analysis by BMI categories and childhood asthma or wheeze. Maternal obesity by BMI categories was significantly associated with asthma or wheeze ever and current asthma or wheeze during childhood. Maternal overweight categories showed nonsignificant trends toward increased asthma or wheeze. Note that ORs are for each category as compared with the “normal weight” category (BMI ~18.5–24.9). Some studies had 2 subgroups (with and without family history of asthma or atopy) and may have 2 entries for the same weight category. Maternal underweight was not significantly associated with childhood asthma or wheeze.

was not associated with asthma or wheeze ($P = .71$).

Figure 3 shows the pooled analysis of maternal BMI and asthma or wheeze. In this analysis, maternal BMI was significantly associated with higher odds of asthma or wheeze ever (OR = 1.03 per each 1 kg/m² increase; 95% CI,

1.02–1.05; $P < .001$) and current asthma or wheeze (OR = 1.02 per kg/m²; 95% CI, 1.01–1.04; $P = .009$). There was significant heterogeneity for both outcomes (asthma or wheeze ever, $I^2 = 70.4\%$; current asthma or wheeze, $I^2 = 66.3\%$). The Egger test showed there could be significant publication

bias for asthma or wheeze ever ($P = .04$) but not for current asthma or wheeze ($P = .99$).

Gestational Weight Gain

Table 1 shows the original studies with GWG as reported (categories or continuous). Figure 4 shows the pooled

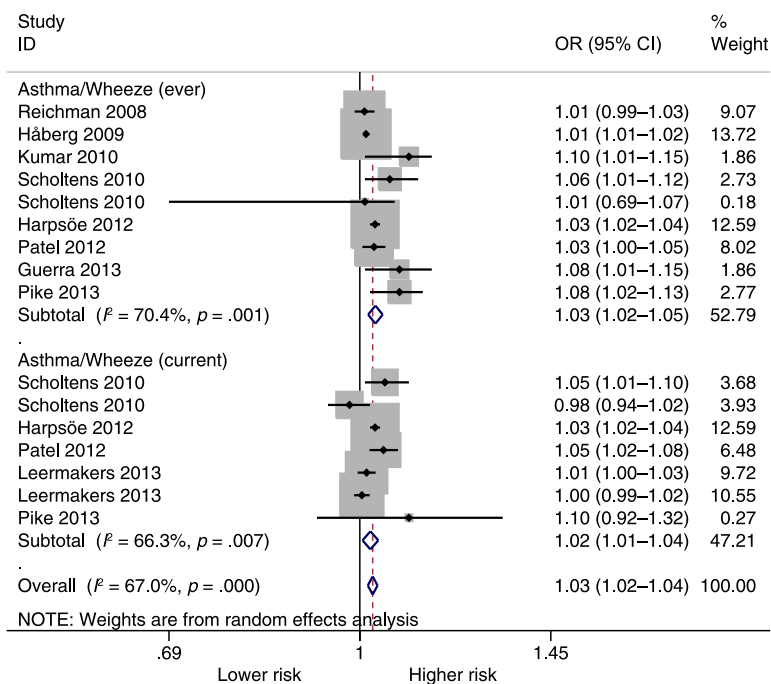


FIGURE 3

Pooled analysis by continuous BMI and asthma or wheeze. Increasing maternal BMI was significantly associated with both asthma or wheeze ever and current asthma or wheeze during childhood. Note that ORs are for each unit increase in BMI. Some studies^{23,29} had 2 subgroups (with and without family history of asthma or atopy) and may have 2 entries.

analysis by reported GWG categories. Children whose mothers were in the higher GWG categories had significantly higher odds of asthma or wheeze ever (OR = 1.16; 95% CI, 1.001–1.34; $P = .049$) but not of current asthma or wheeze (OR = 1.08; 95% CI, 0.89–1.31; $P = .45$). Figure 5 shows the pooled analysis of maternal (continuous) GWG and asthma or wheeze. In this analysis, maternal GWG was significantly associated with higher odds of current asthma or wheeze (OR = 1.015 per 1-kg increase in GWG; 95% CI, 1.01–1.02; $P < .001$) but not with asthma or wheeze ever (OR = 1.04 per kg; 95% CI, 0.97–1.11; $P = .27$). Both for GWG categories and for continuous GWG, the number of studies was small ($n = 2$ – 3). The Egger test showed no significant evidence of publication bias for current asthma or wheeze ($P = .52$), but it could not be calculated for asthma or wheeze ever because of the small number of studies. Subnormal GWG was not associated with asthma

or wheeze ($P = .19$; Supplemental Figure 7), but the number of studies reporting was small ($n = 3$).

Subgroup Analysis and Meta-regression

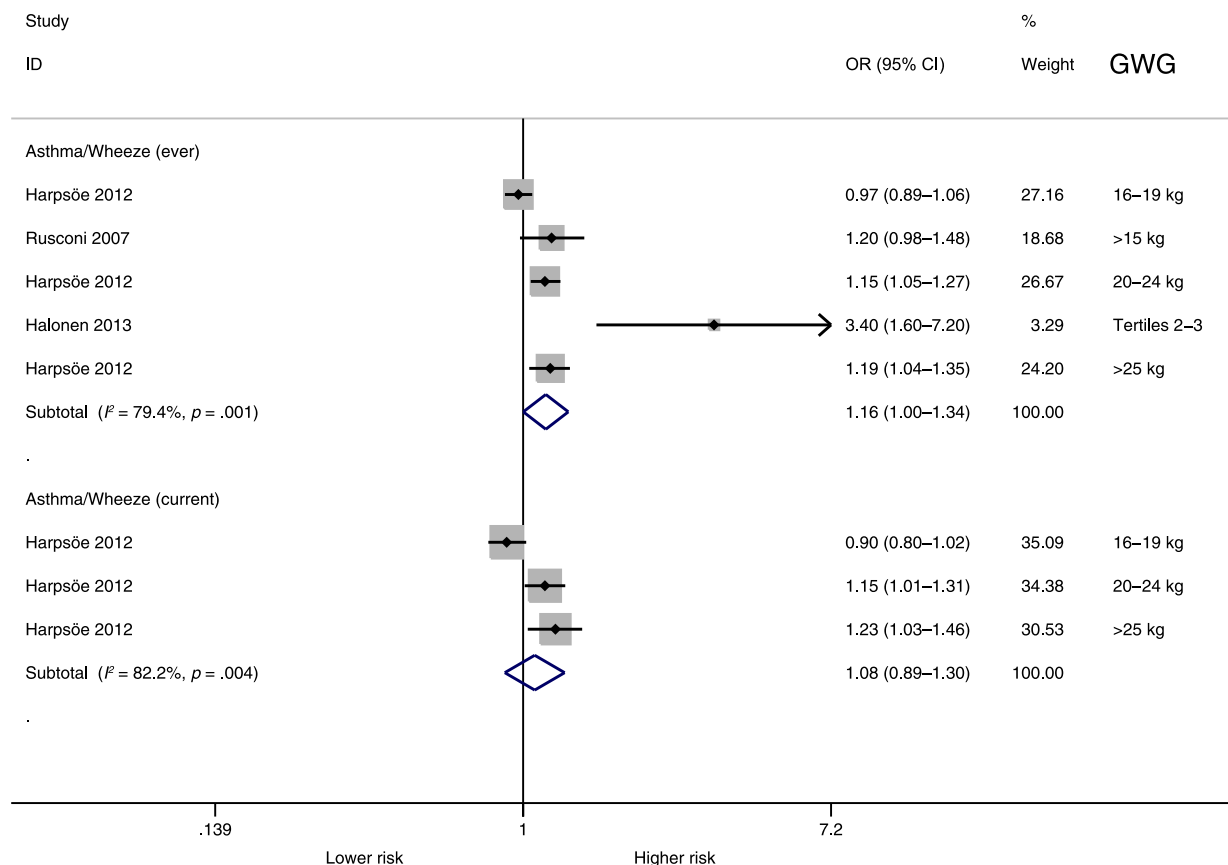
Meta-regression was performed for BMI with covariates available for extraction from the original studies (at the study level [eg, mean or median maternal age in the study] or at the category level when available [eg, mean or median maternal age within each BMI category in the study]). For continuous BMI, meta-regression showed a negative association of borderline significance between maternal history of asthma and the study effect size: The risk of childhood asthma or wheeze with increasing maternal BMI was higher when the prevalence of maternal asthma was lower ($\beta = 0.90$; 95% CI, 0.80–1.01; $P = .07$); this effect modification explained part of the study heterogeneity (I^2 decreased to 33.6%; $R^2 = 81.5\%$). We were unable to perform

subgroup analysis or meta-regression for GWG because of the small number of studies.

DISCUSSION

In this meta-analysis, we report that children whose mothers were obese during pregnancy (defined by BMI categories or by higher continuous BMI) are at higher risk of asthma or wheeze. Maternal underweight did not appear to increase the risk of asthma or wheeze in childhood, although this analysis included only a few studies with small sample sizes and may have been underpowered.

Maternal obesity could influence the risk of asthma in the offspring through several mechanisms. Obesity is associated with a chronic, low-grade inflammatory state.³¹ For example, it has been associated with elevated levels of inflammatory cytokines implicated in asthma, such as tumor necrosis factor α (TNF- α), interleukin 6, and transforming growth factor β -1. Leptin, a proinflammatory adipokine, not only is elevated in the maternal circulation of pregnant obese women but also is higher in the cord blood of their children than in children whose mothers are not obese.³² Conversely, adiponectin, which has antiinflammatory properties and has shown inverse associations with asthma symptoms³³ and airway inflammation,³⁴ is decreased in obesity and is also decreased in newborns of obese mothers.³⁵ Alternatively, maternal obesity may influence the pathogenesis of asthma through exposure of the developing fetus to different dietary patterns.³⁶ For example, obese women are more likely to have low serum levels of vitamin D,³⁷ and maternal vitamin D insufficiency or deficiency has been associated with elevated risk of childhood asthma.³⁸ Similarly, maternal consumption of other foods during pregnancy (eg, meat, dairy, or fats) has

**FIGURE 4**

Pooled analysis by GWG categories and asthma or wheeze. High maternal GWG was significantly associated with asthma or wheeze ever but not with current asthma or wheeze ($P = .47$) during childhood. Note that categories of GWG vary between studies. Subnormal GWG was not significantly associated with childhood asthma or wheeze (see Supplemental Fig 7).

been associated with childhood asthma.^{39,40} Finally, shared genetic polymorphisms or epigenetic changes as a result of maternal obesity could be causing, mediating, or modifying the elevated risk of asthma in their offspring.

Individual studies assessing whether maternal history of asthma modifies the effect of MOP on childhood asthma have shown conflicting results.^{23,25,29} In our meta-regression analysis, there was significant modification of the effect of MOP on asthma by maternal asthma: There was a more pronounced increase in the risk of childhood asthma when the prevalence of maternal asthma was lower. Although such analysis is only exploratory and should be interpreted with caution, it could indicate that the risk conferred

by the mother's asthma supersedes that conferred by maternal obesity. The heritability of asthma has been estimated to be $\sim 0.82\text{--}0.91$,^{12,41} and studies with higher prevalence of maternal asthma could be underpowered to detect an effect of maternal obesity. Alternatively, this finding may suggest that the risk from maternal obesity is stronger for nonatopic asthma. Many^{42–44} but not all⁴⁵ studies of obesity and asthma have reported this association to be stronger among nonatopic children or adults.

GWG was reported in fewer studies. Although there seems to be a higher risk of asthma or wheeze with higher GWG, the observed associations varied depending on the way the exposure was reported (categorical or continuous GWG) and the definition of asthma or

wheeze. GWG has also been associated with elevated maternal^{46,47} and cord blood⁴⁷ leptin levels. Halonen et al²⁰ reported that persistently elevated TNF- α from birth to 3 months of age was associated with asthma and decreased lung function at age 9 years and that maternal GWG was the strongest predictor of an elevated TNF- α level. These findings suggest that GWG and maternal obesity may contribute to the onset of childhood asthma via similar proinflammatory mechanisms. Additional studies are needed to reach more definitive conclusions in regard to GWG and childhood asthma or wheeze.

Studies addressing maternal obesity and childhood asthma that did not meet inclusion criteria for our meta-analysis should be mentioned. In a Swedish

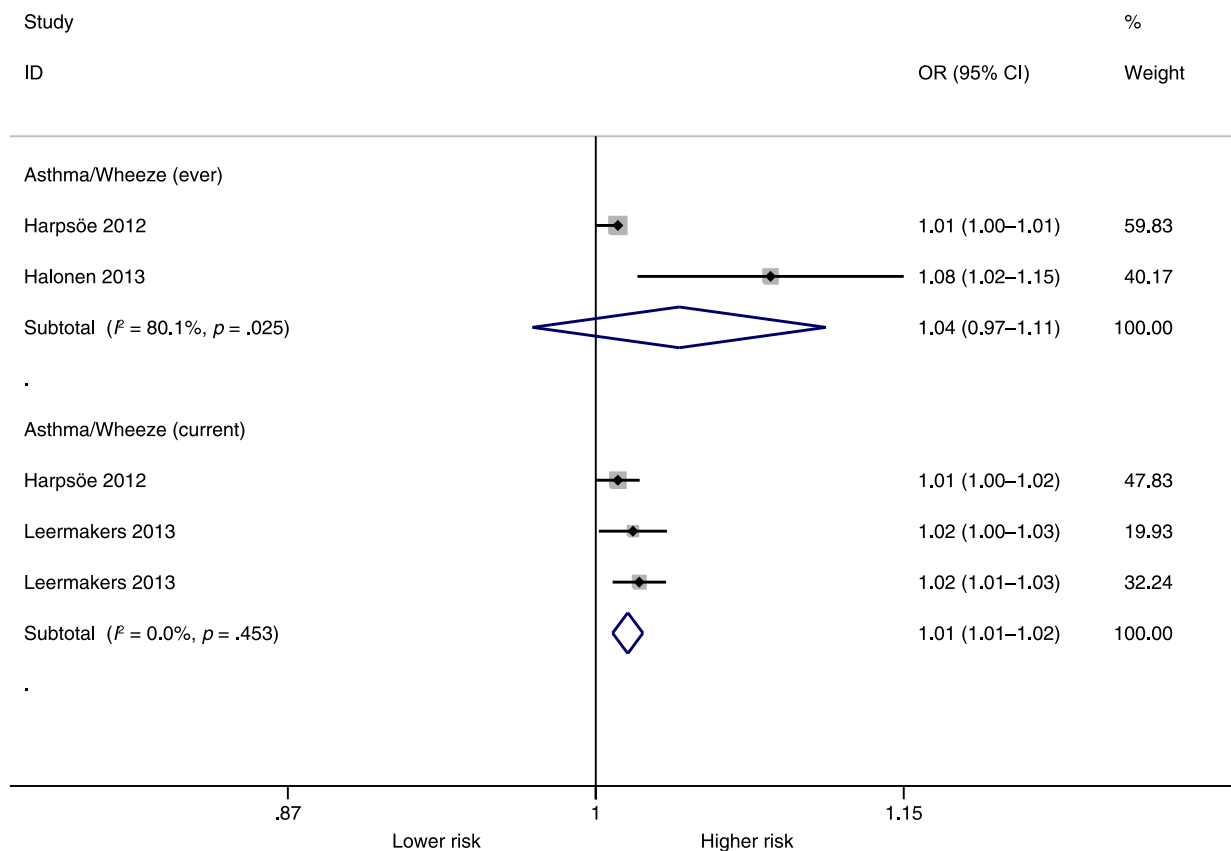


FIGURE 5

Pooled analysis by continuous GWG and asthma or wheeze. Increasing GWG (in kg) was significantly associated with current asthma or wheeze but not with asthma or wheeze ever ($P = .27$) during childhood. Note that ORs are for each 1-kg increase in GWG. Note the small number of studies in each outcome ($n = 2$).

cohort of ~431 000 first-born children, Lowe et al⁴⁸ reported that MOP was associated with greater use of inhaled corticosteroid use in boys and girls up to age 12 years and in girls up to age 16 years; these results suggest that MOP may also be a risk factor for more severe or persistent childhood asthma. Furthermore, in a study by Watson and McDonald,⁴⁹ both maternal baseline skinfold thickness (as a surrogate of percentage body fat) and increase in skinfold thickness during pregnancy were independently associated with greater risk of asthma in childhood, whereas BMI was not significant. The authors proposed that skinfold measurement may be more sensitive than BMI; this extends to maternal obesity in our recent report that for studies of asthma, the child's BMI may not be the best or sole indicator of adiposity.⁴⁵

The current study has several limitations. We included only articles published in English or with sufficient information in English to abstract data for analysis, which may not fully represent all studies conducted on the subject. There was high variability among studies. We dealt with this variability in 3 ways: To account for effect size variability, we used random effects models; to account for the variability in the way BMI and GWG were categorized in the original studies, we obtained effect sizes using continuous BMI or GWG from many of the authors of the original reports; and we performed meta-regression analyses to detect significant effect modifiers. However, as with any meta-analysis, we were limited to the covariates available to us from the original articles. Finally, maternal obesity is also a risk factor for

childhood obesity, and the elevated risk of asthma could result partly from the child's own obesity; however, such confounding is unlikely given that most of the included studies adjusted for birth weight^{16,17,22,23,25,26,29,30} or for the child's weight or BMI at the time of assessment of the outcome.^{17,23,25,27,29}

CONCLUSIONS

We report that MOP is a significant risk factor for the development of childhood asthma or wheeze. GWG may also increase the risk of childhood asthma or wheeze, but we were limited by the small number of studies. The effect of maternal obesity on childhood asthma may be more pronounced when the prevalence of maternal asthma is lower.

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