

Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: A study within the Danish National Birth Cohort

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Background: High pre-pregnancy body mass index (BMI) and excessive gestational weight gain (GWG) are suggested to influence risk of asthma and atopic disease in offspring. **Objective:** We examined the effect of BMI and GWG on risk of asthma, wheezing, atopic eczema (AE), and hay fever in children during the first 7 years of life.

Methods: This was a cohort study of 38,874 mother-child pairs from the Danish National Birth Cohort (enrollment 1996-2002) with information from the 16th week of pregnancy and at age 6 months, 18 months, and 7 years of the child. Odds ratios (ORs) with 95% CIs were calculated by logistic regression with adjustment for potential confounders.

Results: During the first 7 years of life, 10.4% of children developed doctor-diagnosed asthma, 25.8% AE, and 4.6% hay fever. Maternal BMI and to a lesser extent GWG were associated with doctor-diagnosed asthma ever. In particular, BMI ≥ 35 (adjusted OR, 1.87; 95% CI, 0.95-3.68) and GWG ≥ 25 kg (adjusted OR, 1.97; 95% CI, 1.38-2.83) were associated with current severe asthma at age 7 years. Maternal BMI was also associated with wheezing in offspring, with the strongest association observed between BMI ≥ 35 and late-onset wheezing (adjusted OR, 1.87; 95% CI, 1.28-2.73). Maternal BMI and GWG were not associated with AE or hay fever. **Conclusions:** Maternal obesity during pregnancy was associated with increased risk of asthma and wheezing in offspring but not with AE and hay fever, suggesting that pathways may be nonallergic. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Obesity, pre-pregnancy BMI, gestational weight gain, asthma, wheezing, atopy

Obesity is a growing problem worldwide,¹ also during child-bearing years,^{2,3} and women are increasingly gaining excess

Abbreviations used

AE: Atopic eczema
BMI: Pre-pregnancy body mass index
DNBC: Danish National Birth Cohort
GWG: Gestational weight gain
OR: Odds ratio

weight during pregnancy.⁴ Parallel to the rising obesity prevalence, an increase in allergic diseases, including asthma, atopic eczema (AE), and hay fever, has been observed.⁵ Today, obesity is considered to be a condition of chronic low-grade systemic inflammation according to observations of abnormal cytokine production⁶⁻⁹ and an increase in acute-phase reactants, such as C-reactive protein¹⁰ among obese persons. In obesity, the secretion of leptin and adiponectin, the 2 most notable adipokines, is increased¹¹ and decreased,¹² respectively. Leptin is proinflammatory,^{7,13} has been associated with current asthma,¹⁴ atopic¹⁵ and nonatopic¹⁶ asthma, and may increase airway responsiveness and exacerbate asthma.¹³ In contrast, adiponectin is anti-inflammatory and attenuates allergic airway inflammation and hyperresponsiveness.¹⁷ These obesity-related changes in inflammatory factors are suggested to lead to lowered immunologic tolerance to antigens, skewing the immune system toward the allergic T_H2 cytokine profile.⁵

It remains, however, uncertain whether pre-pregnancy body mass index (maternal BMI; calculated as weight divided by height; kg/m²) or excessive weight gain during pregnancy affect the offspring's risk of asthma and allergic diseases through fetal programming. Immune and lung development mainly takes place *in utero* and during early childhood,^{18,19} and leptin receptors have been described in human lung tissue,¹⁵ suggesting an association between leptin and respiratory diseases. A few studies have investigated and found a positive association between maternal BMI and risk of childhood asthma or wheezing,²⁰⁻²⁵ but none of the studies adjusted for gestational weight gain (GWG). However, 2 studies have studied GWG and asthma/wheezing without taking BMI into account.^{26,27} The mutual adjustment of BMI and GWG is essential because these 2 variables are well known to confound each other.²⁸ Still, the current literature does not provide a comprehensive insight into the effect of both BMI and GWG (within the same persons) on *both* respiratory and allergic diseases in children *and* taking into account childhood BMI and atopic sensitization.

The aim of the present study was therefore to examine the combined associations of maternal BMI and GWG with asthma, wheezing, AE, and hay fever in children during the first 7 years of life, using the large population-based Danish National Birth Cohort (DNBC).

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Supported by a Female Research Leader grant (no.09-066323) from the Danish Council of Independent Research to T.J. and by an ERC Starting Grant (ERC-2009-StG-243149) to C.S.B. The funding source had no role in the project.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 20, 2012; revised August 28, 2012; accepted for publication September 13, 2012.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2012.09.008>

METHODS

Study population

Between 1996 and 2002, 100,419 pregnancies were enrolled in the DNBC by asking mothers to participate in 4 telephone interviews (at the 16th and 30th week of pregnancy and when the child was 6 and 18 months of age).²⁹ Seven years after birth, the woman filled out a self-administered questionnaire about the health of the child. Information, publications, and questionnaires can be found at <http://www.dnbc.dk>.

In addition to the DNBC questionnaires, we obtained information about birth characteristics, including gestational age and birth weight, from the National Medical Birth Registry, whereas information about disease during pregnancy, such as diabetes and preeclampsia, was retrieved from The National Hospital Discharge Register. Only live born, full-term singletons (≥ 259 days of gestation) and mothers without obesity-related pregnancy complications (preeclampsia and diabetes) were included in this study (as described in detail in a previous study of GWG in DNBC²⁸). This led to the exclusion of 14,850 pregnancies. Excluding subjects missing information about BMI and GWG from the first and third interviews ($n = 24,570$) and mother-child pairs that did not participate in the 7-year follow-up ($n = 22,125$) resulted in a study population of 38,874 children of 37,164 mothers.

Exposures

Maternal BMI was constructed from self-reported and formerly validated³⁰ weight and height measures from interview 1 and categorized according to definitions from the World Health Organization³¹ as displayed in Table I. These groups will be referred to as underweight ($\text{BMI} < 18.5$), normal weight ($18.5 \leq \text{BMI} < 25$ [reference]), overweight ($25 \leq \text{BMI} < 30$), obese ($30 \leq \text{BMI} < 35$), and very obese ($\text{BMI} \geq 35$). GWG was based on the question "How much (in kg) was your total weight gain in pregnancy?" posed in interview 3. The variable was divided into 6 categories, as seen in Table I and as previously described²⁸ with the addition of 2 extreme categories. The reference 10 to 15 kg was chosen because it has been associated with lowest infant mortality in other populations.³²

Outcomes

The information on asthma, wheezing, AE, and hay fever was based on questions from interview 4, conducted when the child had reached 18 months of age and from the 7-year follow-up. The questions mainly follow the International Study of Asthma and Allergies in Childhood core questionnaires.³³

Doctor-diagnosed asthma ever was generated from the 7-year follow-up question: "Has a doctor ever said that your child had asthma?" Previously, the specificity of the question of "physician-diagnosed asthma" has been found to be 99% both in a literature review on adult asthma³⁴ and in a study based on 7- to 8-year-old schoolchildren.³⁵ The following subgroups of asthma in the *asthma ever* group were also based on the 7-year follow-up: *current doctor-diagnosed asthma* (asthma symptoms or medicine in the past 12 months) and *previous doctor-diagnosed asthma* (no current asthma). The categories *current doctor-diagnosed mild asthma* and *current doctor-diagnosed severe asthma* (during the past 12 months) were differentiated on whether the child had experienced asthma-related disturbed sleep or limited speech.

The outcome wheezing consisted of *early transient* (>1 episode of wheezing from birth to age 18 months), *persistent* (both early and current wheezing, including single, early episodes), and *late-onset wheezing* (current but not early) by questions posed when the child was 18 months old and at the 7-year follow-up.

Atopic eczema ever was defined by fulfilling either (1) United Kingdom criteria,³⁶ the most extensively validated diagnostic criteria for AE,³⁷ but slightly modified to fit the questions or (2) a validated algorithm for AE created for a previous DNBC study.³⁸ All children in the subgroups of AE had either been given the AE diagnosis by a doctor or were fulfilling the algorithm. *Current AE* was defined by the child having symptoms within the past 12 months and *previous AE* by only presenting previous symptoms of AE. The periods *early transient*, *persistent*, and *late-onset AE* were constructed by the same principle as wheezing. Children that could not be categorized in periods because of incoherent or missing answers were not included in these analyses (referred to as "not specified AE" in Results).

Doctor-diagnosed hay fever ever was determined by the question "Has a doctor ever told you that your child has hay fever?" from the 7-year follow-up.

Confounders and intermediate variables

The following confounders were chosen *a priori*: sex of the child, maternal age at conception (age < 20 , 20–24, 25–29, 30–34, 35–39, ≥ 40 years), maternal smoking during the first trimester (nonsmoker, < 10 , ≥ 10 cigarettes/d), number of older siblings (0, 1, 2, 3, ≥ 4), and maternal history of allergy (asthma, atopic eczema, and/or hay fever [yes, no]).

As potential confounders, we chose parity, socio-occupational status of parents combined, alcohol in pregnancy, exercise in pregnancy, season of birth (4 seasons), cohabitation (with spouse or other), farm residency (mother living on a farm with livestock), mode of delivery (cesarean section, vaginal delivery), day care at 18 months, and smoking in the presence of the child during the first 6 months of life.

The following variables were considered potential intermediate variables between maternal BMI and GWG and risk of disease: gestational age ($37 \leq \text{age} < 39$, $39 \leq \text{age} < 42$, ≥ 42 weeks), birth weight (5 groups of each 500 grams: first < 2500 g and fifth ≥ 4000 g), exclusive breast-feeding (none or < 14 weeks, 14–21 weeks, ≥ 22 weeks), and body mass index of the child at the 7-year follow-up (BMI in z-scores, continuous variable based on age- and sex-specific reference values³⁹). All thresholds were based on clinical relevance.

Statistical analysis

With the use of multivariable binomial logistic regression analysis, we calculated odds ratios (ORs) with 95% CIs for the associations between maternal BMI and GWG and the outcomes doctor-diagnosed asthma ever, AE, and doctor-diagnosed hay fever ever. Polytomous logistic regression was used when estimating ORs for subtypes of wheezing, asthma, and AE to allow for test for homogeneity between subtypes. Normal-weight women according to BMI and women with GWG of 10 to 15 kg served as reference.

In adjusted analyses, maternal BMI and GWG were mutually adjusted, confounders selected *a priori* were included as well, whereas the potential confounders were only included if they changed the ORs by $> 10\%$, which was not the case for any of them. In additional analyses, potential intermediate factors were included one by one as covariates. Furthermore, to evaluate residual confounding of the associations between BMI and GWG and odds of doctor-diagnosed asthma ever, we adjusted for GWG and BMI with the use of splines with 5 knots. In addition, we stratified doctor-diagnosed asthma ever and all 3 wheezing categories by whether the child had AE or hay fever versus none of the 2, using these 2 diagnoses as surrogate markers of atopic sensitization in the child.

Robustness analyses, excluding the 1710 mothers with > 1 child in the study, did not change the estimates markedly, and these mother-child pairs were therefore kept in the cohort in all analyses. Tests for homogeneity of ORs were performed in relation to each outcome of interest for BMI and GWG overall as well as by comparing the effect of BMI and GWG, respectively, in the following groups: current versus previous doctor-diagnosed asthma, current doctor-diagnosed severe versus mild asthma, and early transient versus persistent versus late-onset wheezing. *A priori* we chose homogeneity tests to allow for U-shaped associations. We tested for interaction between BMI and GWG in relation to doctor-diagnosed asthma ever and wheezing by including an interaction term in adjusted binomial (asthma) and polytomous (wheezing) logistic regression analyses. Tests were all performed by Wald tests.

All data management and analysis were performed with SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

From birth to the 7-year follow-up, 10.4% of the children had doctor-diagnosed asthma, 5.4% of these children were

TABLE I. Prevalence of main outcomes at 7 years according to maternal pre-pregnancy BMI and GWG

	No. of children in the cohort	Doctor-diagnosed asthma ever, no. (%)	Wheezing			Atopic eczema ever, no. (%)	Doctor-diagnosed hay fever ever, no. (%)
			Early transient, no. (%)	Persistent, no. (%)	Late-onset, no. (%)		
Pre-pregnancy BMI							
<18.5	1,658	173 (10.4)	372 (22.4)	36 (2.2)	49 (3.0)	454 (27.4)	74 (4.5)
18.5 ≤ BMI < 25	27,282	2,620 (9.6)	6,254 (22.9)	645 (2.4)	823 (3.0)	7,061 (25.9)	1,252 (4.6)
25 ≤ BMI < 30	7,245	857 (11.8)	1,819 (25.1)	208 (2.9)	257 (3.5)	1,821 (25.1)	335 (4.6)
30 ≤ BMI < 35	2,019	301 (14.9)	555 (27.5)	76 (3.8)	82 (4.1)	530 (26.3)	84 (4.2)
≥35	670	101 (15.1)	189 (28.2)	22 (3.3)	34 (5.1)	146 (21.8)	37 (5.5)
GWG							
<5 kg	793	119 (15.0)	227 (28.6)	218 (2.6)	34 (4.3)	194 (24.5)	34 (4.3)
5-9 kg	3,860	426 (11.0)	906 (23.5)	130 (3.4)	130 (3.4)	957 (24.8)	152 (3.9)
10-15 kg	17,947	1,778 (9.9)	4,183 (23.3)	439 (2.4)	551 (3.1)	4,626 (25.8)	835 (4.7)
16-19 kg	8,230	787 (4.4)	1,923 (23.4)	194 (2.4)	264 (3.2)	2,130 (25.9)	384 (4.7)
20-24 kg	5,451	624 (11.4)	1,314 (24.1)	130 (2.4)	180 (3.3)	1,405 (25.8)	257 (4.7)
≥25 kg	2,593	318 (12.3)	636 (24.5)	73 (2.8)	86 (3.3)	700 (27.0)	120 (4.6)
Totals	38,874	4,052 (10.4)	9,189 (23.6)	987 (2.5)	1245 (3.2)	10,012 (25.8)	1,782 (4.6)

characterised as having current asthma (0.9% severe asthma). Wheezing was divided into early transient (23.6%), persistent (2.5%), and late-onset (3.2%) wheezing. AE ever was found in 25.8% of all children (8.8% early transient, 5.4% persistent, 4.9% late-onset, and 6.7% not specified), and 8.7% had current AE. In addition, 4.6% had doctor-diagnosed hay fever.

Table I shows the number of children with doctor-diagnosed asthma ever, wheezing, AE, and doctor-diagnosed hay fever ever by maternal BMI and GWG. Maternal mean age at conception was 30 years, 24.3% of the mothers smoked in the first trimester, and 21.7% had a history of allergy (asthma, AE, and/or hay fever). Further, 51.0% of the children were boys, and 54.1% had 1 or more older siblings.

Asthma and wheezing

Compared with children of normal-weight mothers, children of mothers with high BMI had significantly increased odds of doctor-diagnosed asthma ever ($P < .0001$; Table II), in particular children of mothers who were obese (adjusted OR, 1.54; 95% CI, 1.34-1.76) or very obese (adjusted OR, 1.52; 95% CI, 1.21-1.91). The odds of doctor-diagnosed asthma ever increased significantly with increasing GWG ($P = .01$) with the highest odds observed among children of mothers gaining ≥25 kg during pregnancy compared with children of mothers gaining 10 to 15 kg (adjusted OR, 1.17; 95% CI, 1.02-1.33). For GWG, the ORs were greatly attenuated by adjustment for *a priori* confounders (adjustment for maternal BMI alone changed the crude OR in GWG <5 kg from 1.62 to 1.25; in GWG 5-9 kg changed the crude OR from 1.13 to 1.04). Of the chosen potential intermediate factors, child BMI at age 7 showed the strongest, but still only a limited, effect on adjusted estimates for both BMI and GWG, as shown for doctor-diagnosed asthma ever (Table II). Adjustment for intermediate variables in analyses of all other outcomes did not change estimates markedly (not shown). Stratifying doctor-diagnosed asthma ever by AE or hay fever ever suggested a tendency toward a stronger association between maternal BMI and doctor-diagnosed asthma ever in children without AE or hay fever than in children with AE or hay fever (Table II). Stratifying early transient, persistent, and late-onset wheezing in the 2 groups showed similar results for increasing maternal BMI, especially

in BMI ≥35 for early transient wheezing (with AE or hay fever: OR, 1.15; 95% CI, 0.84-1.58; without AE or hay fever: OR, 1.41; 95% CI, 1.14-1.73) and late-onset wheezing (with AE or hay fever: OR, 1.28; 95% CI, 0.69-2.38; without AE or hay fever: OR, 2.45; 95% CI, 1.53-3.91), although differences between groups did not reach statistical significance.

Current and previous doctor-diagnosed asthma showed similar associations with BMI and GWG as asthma ever. However, GWG appeared to have a stronger effect on current than on previous asthma ($P = .006$; Table III). Moreover, we observed close to 2-fold increased odds of current severe asthma in children of very obese mothers (adjusted OR, 1.87; 95% CI, 0.95-3.68) and mothers with a weight gain of ≥25 kg (adjusted OR, 1.97; 95% CI, 1.38-2.83), whereas the effect of these exposures on current mild asthma was less pronounced, especially for GWG (Table III). Children of mothers with high BMI also had significantly increased odds of early transient, persistent, and late-onset wheezing (Table IV). In particular, the odds of late-onset wheezing was up to 87% increased for children of very obese mothers, although differences in ORs across the 3 wheezing categories for BMI did not reach statistical significance ($P = .61$). We found no significant associations between high GWG and wheezing.

AE and hay fever

BMI and GWG were not significantly associated with AE ever; current, previous, early transient, persistent, or late-onset AE; or doctor-diagnosed hay fever ever in offspring (Table V).

No significant interaction between BMI and GWG (adjusted for *a priori* confounders) was observed for any of the outcomes (doctor-diagnosed asthma ever, early transient wheeze, persistent wheeze, late-onset wheeze, AE ever, doctor-diagnosed hay fever ever). In addition, to investigate whether U-shaped associations were present, we replaced the categorical variables (BMI and GWG) with continuous ones in an alternative trend test model. These variables were used as linear and squared terms in the same adjusted analyses. Squared BMI did not show significant for any outcomes, but in doctor-diagnosed asthma ever, previous doctor-diagnosed asthma, current doctor-diagnosed asthma, current doctor-diagnosed severe asthma, and late-onset wheezing

TABLE II. ORs of doctor-diagnosed asthma ever ($n = 4052$) during the first 7 years of life with additional adjustment for potential intermediate variables and stratification by AE according to pre-pregnancy BMI and GWG

	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)* for gestational age	Adjusted OR (95% CI)* for birth weight
Pre-pregnancy BMI [‡]				
<18.5	1.11 (0.95-1.30)	1.05 (0.89-1.24)	1.03 (0.88-1.22)	1.01 (0.86-1.20)
18.5 ≤ BMI < 25	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 ≤ BMI < 30	1.24 (1.15-1.34)	1.21 (1.11-1.32)	1.22 (1.12-1.33)	1.23 (1.13-1.34)
30 ≤ BMI < 35	1.60 (1.41-1.81)	1.54 (1.34-1.76)	1.56 (1.36-1.79)	1.58 (1.38-1.81)
≥35	1.64 (1.33-2.02)	1.52 (1.21-1.91)	1.55 (1.23-1.95)	1.57 (1.24-1.98)
<i>P</i> , test for homogeneity	<.0001	<.0001	<.0001	<.0001
GWG [‡]				
<5 kg	1.62 (1.32-1.98)	1.17 (0.94-1.46)	1.17 (0.94-1.45)	1.14 (0.92-1.42)
5-9 kg	1.13 (1.01-1.27)	1.03 (0.92-1.16)	1.02 (0.91-1.15)	1.01 (0.90-1.42)
10-15 kg	1 (reference)	1 (reference)	1 (reference)	1 (reference)
16-19 kg	0.96 (0.88-1.05)	0.96 (0.88-1.06)	0.97 (0.89-1.06)	0.98 (0.89-1.07)
20-24 kg	1.18 (1.07-1.30)	1.14 (1.03-1.26)	1.15 (1.05-1.27)	1.16 (1.05-1.28)
≥25 kg	1.27 (1.12-1.45)	1.17 (1.02-1.33)	1.19 (1.04-1.35)	1.19 (1.04-1.36)
<i>P</i> , test for homogeneity	<.0001	.01	.004	.005

To evaluate residual confounding, we also adjusted for BMI and GWG using splines and observed similar associations.

*Adjusted for sex of the child, maternal age at conception, maternal smoking during first trimester, number of older siblings, maternal history of allergy, and mutually adjusted for pre-pregnancy BMI and GWG.

[‡]At 7-year follow-up.

[§]No interaction between BMI and GWG was observed (doctor-diagnosed asthma ever; $P = .65$).

GWG analyses were significant, pointing to a U-shaped association.

DISCUSSION

In this population-based study, pre-pregnancy obesity in mothers and excess weight gain during pregnancy were found to be independently associated with asthma and wheezing in the offspring, especially in nonatopic children. The association was strongest for current asthma in children at age 7 years and was not explained by child BMI. In contrast, no association between BMI and GWG and the allergic diseases, AE and hay fever, was observed.

The main strength of this study was the availability of a large, national birth cohort of Danish children and their mothers with detailed information on all variables. In addition, we included information from the Danish Birth Register and the National Hospital Discharge Register to obtain information on diseases during pregnancy and birth characteristics and used interviews that followed questionnaires validated by the International Study of Asthma and Allergies in Childhood. In contrast to previous studies, we were able to include detailed information about both BMI and GWG from the same women, enabling us to study the independent effect of each factor. Another advantage was the inclusion of all 4 immunologically based outcomes, representing airway-related diseases (asthma and wheezing) and allergic/atopic diseases (AE and hay fever), which allowed us to examine the interplay between possibly closely related disease manifestations.

Despite the large sample size and detailed information from the questionnaires, the study also has limitations that require consideration. Self-reporting may lead to misclassification of variables. Among mothers in the United Kingdom, different perceptions of the word “wheezing” in children have

previously been shown,⁴⁰ whereas by contrast, there are data supporting the idea that maternal reports on children's asthma diagnoses correlate well with the children's asthma symptoms.⁴¹ Incomplete recall of the medical diagnoses may especially be a problem in countries that rely on health care insurance⁴²; however, in Denmark all health care is free. Of note, we have used 18 months as cutoff in defining the 3 wheezing periods, why the study is not completely comparable with previous studies that used other and various cutoffs.^{43,44} Furthermore, self-reported weight in women may be underreported, particularly in women with high BMI,⁴⁵ but, if anything, this would most likely attenuate the observed associations toward the null. Likewise, GWG was self-reported 6 months after birth, but all Danish women's weight is closely monitored throughout pregnancy, and the private records are kept by the woman after birth. However, women were not strictly asked to have their private record with them at the time of the interview, so we cannot know if these were used. In a sample of 2389 women within the cohort, we had information about GWG recorded by the midwives at admission at the delivery ward. Comparisons of the 2 data sources showed little systematic difference but considerable variation.⁴⁶ This problem would most likely bias the associations toward the null. As a source of sample selection bias, groups with low socioeconomic resources have been found underrepresented in DNBC,⁴⁷ and participants may thus be somewhat healthier in sense of weight and smoking than the source population,⁴⁸ but all pre-pregnancy BMI and socio-occupational status groups were actually well represented in the present study. Differential loss to follow-up is another limitation to consider. However, outcomes were not known at the time of enrollment and are not assumed to be severe enough to influence participation in the 7-year follow-up. In addition, a previous study investigated

TABLE II. (Continued)

Adjusted OR (95% CI)* for breast-feeding	Adjusted OR (95% CI)* for BMI†	With AE or hay fever (n = 1927) Adjusted OR (95% CI)*	Without AE or hay fever (n = 2082) Adjusted OR (95% CI)*
1.04 (0.89-1.23)	1.06 (0.89-1.26)	1.04 (0.82-1.31)	1.08 (0.87-1.34)
1 (reference)	1 (reference)	1 (reference)	1 (reference)
1.19 (1.10-1.30)	1.16 (1.06-1.26)	1.16 (1.03-1.30)	1.27 (1.14-1.42)
1.49 (1.30-1.71)	1.44 (1.24-1.67)	1.41 (1.17-1.71)	1.63 (1.37-1.96)
1.46 (1.16-1.84)	1.41 (1.09-1.80)	1.45 (1.05-2.00)	1.55 (1.14-2.11)
<.0001	<.0001	.001	<.0001
1.16 (0.93-1.44)	1.18 (0.93-1.49)	1.23 (0.91-1.67)	1.14 (0.85-1.52)
1.03 (0.91-1.15)	1.02 (0.90-1.15)	1.08 (0.92-1.27)	0.99 (0.84-1.16)
1 (reference)	1 (reference)	1 (reference)	1 (reference)
0.96 (0.88-1.05)	0.93 (0.85-1.02)	0.95 (0.84-1.08)	0.96 (0.85-1.09)
1.14 (1.03-1.25)	1.10 (0.99-1.23)	1.13 (0.98-1.29)	1.14 (0.99-1.30)
1.16 (1.01-1.32)	1.12 (0.98-1.29)	1.24 (1.04-1.49)	1.07 (0.91-1.30)
.02	.04	.04	.24

bias due to loss to follow-up in DNBC, linking cohort data with the National Hospital Discharge Register. The study found negligible bias introduced by loss to follow-up in the DNBC, with pre-pregnancy BMI and childhood asthma being 2 of 10 different exposures and outcomes. Overall, it was concluded that bias from loss to follow-up may be quite modest for medical factors that characterises our outcome data.⁴⁹

The findings from this study confirm the positive association between high BMI and wheeze and/or asthma found in 6 other studies.²⁰⁻²⁵ However, all former studies lacked adjustment for GWG, and 3 of them based their results on 3-year-old children,^{20,21,24} an age at which we assume an asthma diagnosis to be less reliable. Only 1 of the 6 studies considered childhood eczema and found eczema unrelated to maternal BMI and inversely associated with cord-blood IgE, a marker in allergy,²¹ suggesting BMI to be mainly associated with nonallergic respiratory illness. This is in line with our finding of no association with AE or hay fever and an association with doctor-diagnosed asthma ever both among atopic but especially nonatopic children. Thereby, the results did not show stronger effects in children with additional allergic disease which could have been the case if maternal obesity affected the child's immune system through an allergic pathway. Further corroborating this notion, increased ORs between high maternal BMI and development of wheezing and asthma have previously been found in adolescents with nonatopic parents but not among adolescents with atopic parents.²³ A stronger association between child obesity and doctor-diagnosed current asthma in nonatopic children compared with atopic children has also been observed.⁵⁰

The effect of GWG on asthma and wheezing has been assessed in 2 previous studies. A small case-control study found GWG <9 kg positively associated with asthma in children aged 4 to 9 years²⁶ but did not consider maternal BMI, which we

found to greatly attenuate the association between GWG <10 kg and doctor-diagnosed asthma ever. Rusconi et al²⁷ did not find GWG <9 kg or >15 kg to be significantly associated with wheezing, parallel to our findings for GWG even though our findings show a U-shaped tendency. Note, data of this previous study were collected retrospectively when the child was 6 to 7 years of age and weight change in pregnancy along with early symptoms in the child may therefore be subject to recall bias. Most importantly, neither of the former 2 studies of GWG took BMI into consideration, provided no information on very high or very low GWG, and addressed only 1 respiratory outcome each. With much greater detail and adjustment for BMI, we found that high GWG mainly affects the risk of current severe asthma in the child. Further, the U-shaped tendency between GWG and asthma and wheezing outcomes has not been investigated in previous studies, in which only high or low GWG has been assessed. However, our findings correspond well with the known U-shaped relation between body mass index and risk of other acute and chronic diseases as well as mortality.⁵¹⁻⁵³ Our results are also in accordance with the findings by Olivetti et al²⁶ of an increased risk of asthma with low GWG. Further, no significant interaction was found between BMI and GWG; why the increased odds found in low GWG categories do not reflect an underlying high BMI.

Childhood obesity has previously been found to influence the risk of asthma and wheezing,^{54,55} but only a limited number of previous studies of maternal BMI or GWG took this variable into account.^{21,25} In this study we were able to show that the effect of maternal BMI and GWG on risk of asthma and wheezing in offspring only to a limited degree is explained by obesity passed on from mother to child.

Herberth et al⁵⁶ examined the effect of maternal immune responses in pregnancy on children's immune system and found

TABLE III. ORs of previous and current doctor-diagnosed asthma during the first 7 years of life according to pre-pregnancy BMI and GWG

	Previous (n = 1961)		Current (n = 2091)	
	Adjusted OR (95% CI)†	Adjusted OR (95% CI)†	Severe* (n = 346) Adjusted OR (95% CI)†	Mild* (n = 1594) Adjusted OR (95% CI)†
Pre-pregnancy BMI				
< 18.5	1.02 (0.81-1.29)	1.07 (0.85-1.34)	1.08 (0.63-1.87)	0.97 (0.74-1.26)
18.5 ≤ BMI < 25	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 ≤ BMI < 30	1.19 (1.05-1.33)	1.24 (1.10-1.38)	1.44 (1.11-1.87)	1.19 (1.05-1.36)
30 ≤ BMI < 35	1.50 (1.24-1.81)	1.58 (1.32-1.90)	1.73 (1.14-2.61)	1.55 (1.26-1.90)
≥35	1.55 (1.14-2.11)	1.48 (1.08-2.04)	1.87 (0.95-3.68)	1.42 (0.99-2.05)
P, test for homogeneity	<.0001	<.0001	.01	.0001
GWG				
<5 kg	1.54 (1.17-2.03)	0.84 (0.60-1.17)	0.90 (0.42-1.92)	0.88 (0.61-1.27)
5-9 kg	0.94 (0.80-1.12)	1.11 (0.96-1.29)	1.44 (1.02-2.03)	1.05 (0.88-1.25)
10-15 kg	1 (reference)	1 (reference)	1 (reference)	1 (reference)
16-19 kg	1.03 (0.91-1.17)	0.90 (0.80-1.02)	1.03 (0.76-1.40)	0.90 (0.78-1.03)
20-24 kg	1.13 (0.99-1.30)	1.15 (1.01-1.31)	1.31 (0.95-1.81)	1.11 (0.96-1.30)
≥25 kg	1.11 (0.93-1.33)	1.23 (1.03-1.46)	1.97 (1.38-2.83)	1.03 (0.83-1.27)
P, test for homogeneity	.01	.0003	.003	.20

Test for homogeneity comparing ORs of previous and current asthma, BMI, $P = .67$; GWG, $P = .006$.

Test for homogeneity comparing ORs of current severe and mild asthma, BMI, $P = .98$; GWG, $P = .06$.

*Severe and mild asthma do not add up to the total number of current doctor-diagnosed asthma because of missing answers in the 7-year follow-up.

†Adjusted for sex of the child, maternal age at conception, maternal smoking during first trimester, number of older siblings, maternal history of allergy, and mutually adjusted for pre-pregnancy BMI and GWG.

TABLE IV. ORs of early transient, persistent, and late-onset wheezing during the first 7 years of life according to pre-pregnancy BMI and GWG

	Early transient wheezing (n = 9189)		Persistent wheezing (n = 987)		Late-onset wheezing (n = 1245)	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Pre-pregnancy BMI†						
<18.5	0.97 (0.86-1.09)	0.94 (0.83-1.06)	0.91 (0.65-1.28)	0.81 (0.57-1.15)	0.97 (0.72-1.30)	0.96 (0.71-1.30)
18.5 ≤ BMI < 25	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 ≤ BMI < 30	1.15 (1.08-1.22)	1.13 (1.06-1.20)	1.28 (1.09-1.50)	1.19 (1.01-1.40)	1.24 (1.07-1.43)	1.22 (1.05-1.41)
30 ≤ BMI < 35	1.34 (1.21-1.49)	1.29 (1.16-1.44)	1.78 (1.39-2.27)	1.62 (1.26-2.09)	1.50 (1.19-1.90)	1.48 (1.16-1.89)
≥35	1.42 (1.19-1.69)	1.33 (1.10-1.60)	1.60 (1.04-2.48)	1.44 (0.91-2.28)	1.94 (1.36-2.77)	1.87 (1.28-2.73)
P, test for homogeneity	<.0001	<.0001	<.0001	.0006	<.0001	.0002
GWG†						
<5 kg	1.36 (1.16-1.60)	1.13 (0.95-1.34)	1.20 (0.77-1.87)	0.82 (0.51-1.32)	1.55 (1.08-2.21)	1.14 (0.78-1.67)
5-9 kg	1.03 (0.95-1.12)	0.99 (0.91-1.08)	1.41 (1.15-1.72)	1.24 (1.01-1.53)	1.12 (0.92-1.36)	1.04 (0.85-1.27)
10-15 kg	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
16-19 kg	1.00 (0.94-1.07)	1.01 (0.95-1.07)	0.96 (0.81-1.15)	0.99 (0.83-1.18)	1.05 (0.90-1.22)	1.09 (0.93-1.26)
20-24 kg	1.06 (0.98-1.13)	1.03 (0.96-1.11)	1.00 (0.82-1.21)	0.96 (0.79-1.18)	1.10 (0.92-1.30)	1.12 (0.94-1.33)
≥25 kg	1.09 (0.99-1.20)	1.04 (0.94-1.15)	1.19 (0.92-1.53)	1.12 (0.86-1.45)	1.12 (0.88-1.41)	1.14 (0.90-1.44)
P, test for homogeneity	.004	.68	.01	.23	.21	.71

Test for homogeneity comparing ORs of all three wheezing categories, BMI, $P = .61$; GWG, $P = .36$.

*Adjusted for sex of the child, maternal age at conception, maternal smoking during first trimester, number of older siblings, maternal history of allergy, and mutually adjusted for pre-pregnancy BMI and GWG.

†No interaction between BMI and GWG was observed (wheezing, $P = .54$).

maternal inflammatory cytokines to correlate with the offspring's cytokine level but not with total or allergen-specific IgE or atopic dermatitis.⁵⁶ Furthermore, a recent genome-wide association study found loci associated with the IgE level to play only a minor role in the development of asthma.⁵⁷ The hypothesis of a skewing toward the allergic T_H2 cytokine profile as explanation of our findings is therefore not supported by our study or these previous studies. However, adipokine and cytokine changes in obesity passed on from mother to child could explain some of the suggested effect of BMI and GWG on

asthma and wheezing in the offspring. These observations combined with the findings of this study lead us to hypothesize a nonallergic inflammatory pathway behind the associations between maternal obesity and respiratory symptoms.

In conclusion, this large-scale nationwide birth cohort study is the first to investigate the association between *both* BMI and GWG as exposures and *both* respiratory (asthma and wheezing) and allergic (AE and hay fever) diseases as outcomes, thereby enabling a thorough examination of potential associations. Our findings support the hypothesis that the growing

TABLE V. ORs of AE, subdivided into periods, and doctor-diagnosed hay fever all during the first 7 years of life according to pre-pregnancy BMI and GWG

		Atopic eczema (n = 10,012)					Doctor-diagnosed hay fever ever (n = 1782), adjusted OR (95% CI)*
		Adjusted OR (95% CI)*	Current (n = 3368), adjusted OR (95% CI)*	Previous (n = 6644), adjusted OR (95% CI)*	Early transient (n = 3429)†, adjusted OR (95% CI)*	Persistent (n = 2115)†, adjusted OR (95% CI)*	
Pre-pregnancy BMI							
<18.5	1.09 (0.97-1.22)	1.19 (1.01-1.41)	1.04 (0.91-1.18)	1.11 (0.93-1.32)	1.16 (0.94-1.43)	1.21 (0.97-1.50)	1.01 (0.79-1.29)
18.5 ≤ BMI < 25	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 ≤ BMI < 30	0.96 (0.90-1.02)	1.00 (0.91-1.10)	0.94 (0.88-1.01)	0.95 (0.86-1.04)	0.96 (0.85-1.08)	1.02 (0.90-1.16)	1.02 (0.90-1.16)
30 ≤ BMI < 35	1.02 (0.91-1.13)	1.06 (0.90-1.25)	1.00 (0.88-1.13)	0.93 (0.78-1.11)	0.95 (0.77-1.17)	1.25 (1.02-1.53)	0.93 (0.74-1.17)
≥35	0.80 (0.66-0.97)	0.75 (0.54-1.03)	0.82 (0.65-1.03)	0.76 (0.55-1.04)	0.65 (0.43-0.97)	1.03 (0.72-1.48)	1.27 (0.89-1.82)
P, test for homogeneity	.05	.08	.23	.20	.13	.12	.66
GWG							
<5 kg	0.97 (0.82-1.16)	1.07 (0.81-1.39)	0.93 (0.75-1.14)	0.89 (0.66-1.18)	1.15 (0.83-1.60)	1.00 (0.72-1.41)	0.90 (0.62-1.31)
5-9 kg	0.97 (0.89-1.05)	0.96 (0.84-1.09)	0.97 (0.88-1.07)	0.95 (0.84-1.08)	0.97 (0.83-1.14)	1.02 (0.86-1.20)	0.85 (0.71-1.02)
10-15 kg	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
16-19 kg	1.00 (0.94-1.06)	0.99 (0.90-1.09)	1.01 (0.94-1.08)	1.04 (0.95-1.14)	0.96 (0.85-1.08)	1.00 (0.88-1.05)	0.98 (0.86-1.11)
20-24 kg	1.00 (0.94-1.08)	1.16 (1.04-1.29)	0.93 (0.85-1.01)	0.94 (0.84-1.05)	1.09 (0.95-1.24)	1.17 (1.02-1.34)	0.98 (0.85-1.14)
≥25 kg	1.06 (0.97-1.17)	1.12 (0.97-1.30)	1.03 (0.93-1.15)	1.00 (0.86-1.16)	1.18 (0.99-1.40)	1.01 (0.83-1.24)	0.95 (0.78-1.16)
P, test for homogeneity	.77	.05	.49	.61	.25	.37	.66

*Adjusted for sex of the child, maternal age at conception, maternal smoking during first trimester, number of older siblings, maternal history of allergy, and mutually adjusted for pre-pregnancy BMI and GWG.

†The number of subjects in the 3 periods of AE does not add up to AE ever because of missing answers in interview 4 and 7-year follow-up.

prevalence of childhood asthma and wheezing can be partly explained by the increase in pre-pregnancy BMI and to a lesser extent by excess weight gain during pregnancy. The pathway seems nonallergic and not acting through child obesity, why mechanisms behind our observations need further investigations but should be considered in prevention of pediatric respiratory illness.

Key messages

- Maternal pre-pregnancy body mass index and to a lesser extent gestational weight gain were independently associated with development of asthma and wheezing in children, almost irrespective of child body mass index but strongest in nonatopic children.
- Maternal obesity was, however, not associated with the allergic diseases, atopic eczema and hay fever.
- This advocates for a nonallergic inflammatory pathway to asthma and wheezing initiated in utero because of maternal obesity-related inflammation.

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