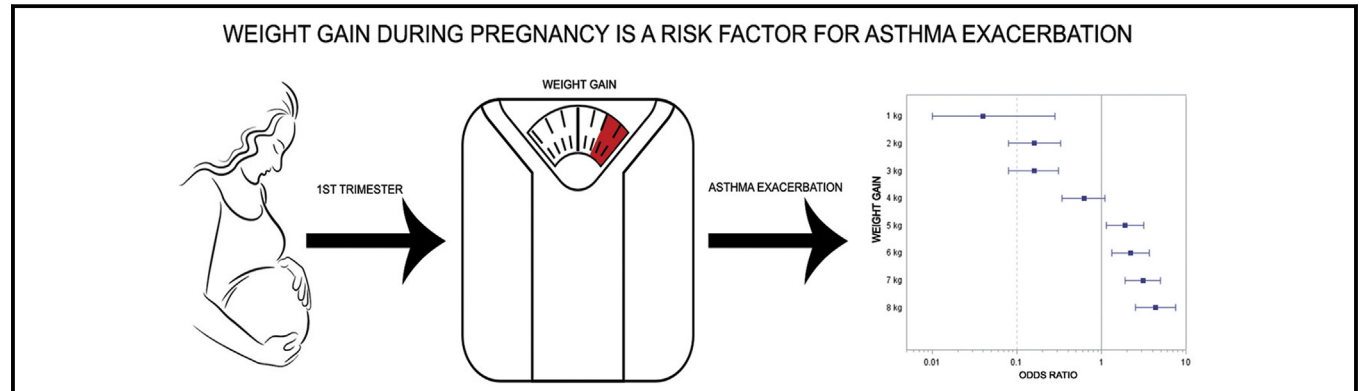


Excessive gestational weight gain in first trimester is a risk factor for exacerbation of asthma during pregnancy: A prospective study of 1283 pregnancies

Zarqa Ali, MD,^a Lisbeth Nilas, DMSc,^{b,c} and Charlotte Suppli Ulrik, DMSc^{a,c}

Hvidovre and Copenhagen, Denmark

GRAPHICAL ABSTRACT



Background: Acute exacerbation during pregnancy is the most important risk factor for an unfavorable outcome of pregnancy in women with asthma.

Objective: We sought to identify pregnancy-related risk factors for acute exacerbations of asthma during pregnancy.

Methods: Since 2007, all pregnant women referred to give birth at Hvidovre Hospital, Denmark, have been offered participation in the prospective Management of Asthma during Pregnancy (MAP) program. Women were included in the present analysis if they fulfilled the following criteria: (1) diagnosed with asthma, (2) prescribed at least rescue bronchodilator, and (3) had the first visit to the respiratory outpatient clinic within the first 18 weeks of pregnancy. Data were analyzed using multiple logistic regression models with backward stepwise elimination (Proc Logistic procedure in SAS).

Results: Over an 8-year study period, a total of 1283 pregnancies in 1208 women fulfilled the criteria for inclusion in the MAP cohort. Women with asthma exacerbation(s) had

larger gestational weight gain (GWG) in the first trimester of pregnancy ($P < .001$) and increased total GWG ($P < .001$) compared with women without exacerbation. More than 5 kg first-trimester weight gain was associated with an increased risk of asthma exacerbation (odds ratio, 9.35; 95% CI, 6.39-13.68; $P < .001$), and the risk increased in a dose-dependent manner with additional weight gain in excess of 5 kg.

Conclusions: Excessive GWG in the first trimester is a risk factor for asthma exacerbation during pregnancy and the risk increases in a dose-dependent manner with increasing GWG. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: Asthma, exacerbation, pregnancy, gestational weight gain

At least one-third of pregnant women with asthma experience an exacerbation during pregnancy, and acute exacerbations are associated with unfavorable pregnancy outcome.¹⁻³ In addition, the prevalence of asthma,⁴ obesity,⁵ and excessive gestational weight gain (GWG) during pregnancy⁶ has been increasing over the last few decades. Maternal obesity is associated with a higher risk of asthma exacerbation during pregnancy⁷ and also with a higher risk of asthma in the offspring.⁸ It has been suggested that maternal obesity may contribute to both maternal and childhood asthma.^{9,10}

Excessive GWG has been associated with an elevated risk of childhood asthma.¹¹ Furthermore, it has previously been suggested that the effect of both maternal weight and GWG is mediated through proinflammatory mechanisms and elevated TNF- α and leptin levels.^{10,12,13} Asthma is characterized by chronic airway inflammation, and the inflammation caused by excessive GWG during pregnancy may affect maternal asthma through the same proinflammatory mechanisms that cause

From ^athe Department of Pulmonary Medicine, Hvidovre Hospital, Hvidovre, ^bthe Department of Gynaecology and Obstetrics, Hvidovre Hospital, Hvidovre, and ^cthe Institute of Clinical Medicine, University of Copenhagen, Copenhagen.

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Corresponding author: Zarqa Ali, MD, Department of Pulmonary Medicine, 253 Hvidovre Hospital, DK-2650 Hvidovre, Denmark. E-mail: zarqa_ali@hotmail.com. 0091-6749/\$36.00

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Abbreviations used

BMI: Body mass index
GINA: Global Initiative for Asthma
GWG: Gestational weight gain
ICS: Inhaled corticosteroid
MAP: Management of Asthma during Pregnancy
OR: Odds ratio

childhood asthma. The impact of excessive GWG on maternal asthma has, however, not been studied systematically.

We hypothesized that excessive GWG may affect maternal asthma during pregnancy. The aim of this study was, therefore, to investigate the impact of maternal pregnancy-related factors, including GWG, on the risk of exacerbations of asthma during pregnancy in a prospective study of a large sample of pregnant women with asthma.

METHODS**Material**

The Management of Asthma during Pregnancy (MAP) program, a prospective research project, was initiated in 2007 and is still ongoing. The overall purpose of the project is to reduce the risk of pregnancy and perinatal complications in women with asthma. Since 2007 pregnant women have consecutively been recruited through the Department of Gynecology and Obstetrics, Hvidovre Hospital. All pregnant women referred to Hvidovre Hospital (~7000 per year, corresponding to 10% of infants born in Denmark every year) were informed about the program as part of the welcome letter from the Department of Gynecology and Obstetrics. The letter included an invitation to participate in the MAP program together with an e-mail address for response (astmaoggraviditet@regionh.dk). All women who accepted the invitation were given a scheduled appointment (by letter) at the outpatient clinic, Department of Pulmonary Medicine.

In the present analysis, women were included provided they fulfilled all of the following inclusion criteria: (1) A diagnosis of asthma, defined according to Global Initiative for Asthma (GINA) guidelines,⁴ (2) current treatment with at least rescue bronchodilator, and (3) first visit to the respiratory outpatient clinic within the first 18 weeks of pregnancy. The participants were prospectively followed from recruitment and seen approximately every 4 weeks during pregnancy and 3 months postpartum. Unscheduled visits were planned if necessary. At the first visit, the following information was collected by the interview: asthma management in relation to pregnancy, case history, tobacco exposure, and present and previously prescribed asthma medication. The importance of adherence with controller medication and sufficient device technique were addressed. Spirometry, fractional exhaled nitric oxide, and maternal body weight were assessed at the first visit and repeated at all subsequent visits. Treatment was adjusted, if necessary, at every visit in accordance with the algorithm later described by Powell et al.¹⁴

Women not fulfilling all inclusion criteria were managed in the same way, but not included in the MAP cohort, and by that not in the present analysis (Fig 1).

Ethics statement

This study was performed in accordance with the Helsinki II declaration and the Danish legislation. The study was approved by the Research Ethics Committee of the Capital Region of Denmark (H-D-2007-0051).

Definitions and methods

Pre-pregnancy maternal body mass index (BMI) was calculated for each participant on the basis of self-reported pre-pregnancy weight in kilograms divided by height² (in meters). GWG in the first trimester of pregnancy was

calculated as the difference between self-reported pre-pregnancy weight and measured weight at the first visit, and the total GWG from self-reported pre-pregnancy weight and measured weight at the last visit before the due date. Postpartum weight loss was calculated as the difference between measured weight at the 3-month postpartum visit and last measured weight during pregnancy. Only women attending the last scheduled visit before delivery were included in postpartum analyses.

Asthma control was assessed on the basis of daytime asthma symptoms, night-time awakenings due to asthma, use of rescue medication, spirometry, and the level of fractional exhaled nitric oxide, and classified as well-controlled or uncontrolled.

On the basis of the prescribed intensity of treatment, the severity of asthma was categorized as mild or moderate/severe according to the GINA guidelines.⁴ Mild asthma was defined as asthma managed with short-acting β_2 agonist as rescue medication with or without low-dose inhaled corticosteroid (ICS) (ie, step 1 or 2 treatment in GINA guidelines). Moderate/severe asthma was defined as asthma treated with any dose of ICS in combination with at least 1 second controller drug, including long-acting β_2 -agonist and/or leukotriene receptor antagonist (step 3, 4, and 5 treatment in GINA guidelines).

Exacerbations were defined according to the American Thoracic Society/European Respiratory Society guidelines on asthma control and exacerbations,¹⁵ and categorized on the basis of severity as mild or severe. Mild exacerbations were defined as exacerbations managed by an increase in therapy, but not requiring oral corticosteroids. Severe exacerbations were defined as exacerbations requiring hospital admission, emergency department treatment, and/or a rescue course of systemic corticosteroid. The information on exacerbations was collected at every visit by asking the women if they had had episodes of worsening of symptoms, changes in prescribed medication, unscheduled contacts to their general practitioner for asthma, and emergency room visits or hospital admissions for asthma since the last visit. Information on unscheduled contacts and prescribed medication, including rescue courses of systemic corticosteroid, was available from medical records.

Statistical analysis

Data analyses were performed using the program editor in SAS Enterprise Guide 7.1 (SAS Institute). Continuous variables were analyzed using the 2-tailed Student *t* test and binary variables were analyzed by using the chi-square test. For each association, a crude model was first analyzed and then adjusted for potential confounders: smoking status (never smoker vs ever smoker), FEV₁ (FEV₁ < 80% or ≥80% of predicted value), treatment with ICS (yes/no), uncontrolled asthma (yes/no), asthma severity (mild vs moderate/severe), pre-pregnancy exacerbations (yes/no), and allergy (yes/no). The impact of first-trimester GWG on risk for exacerbation was furthermore adjusted for nulliparity because nulliparous women have a higher GWG.¹⁶ A multiple logistic regression model with backward stepwise elimination was used with the Proc Logistic procedure in SAS. Variables included in the logistic regression model were the continuous variables: age, pre-pregnancy BMI, total and first-trimester GWG, and the binary variables: sex of the neonate (male yes or no), nulliparity (yes or no), and singleton versus twin pregnancy. The interaction analysis carried out using Proc Genmod procedure in SAS was used to estimate the interaction between GWG and maternal pre-pregnancy BMI.

The last observation of body weight during pregnancy was carried forward for those who did not attend the last visit because of preterm delivery.

Results are given as odds ratios (ORs) with 95% CIs. A *P* value of less than .05 was considered statistically significant.

RESULTS**Patients' characteristics**

A total of 1283 pregnancies in 1208 women were enrolled in the 8-year study period (2007-2015), and the mean gestational age at the first visit at the outpatient clinic was 14 weeks. A total of 468 exacerbations of asthma were observed: 273 (58%) mild and

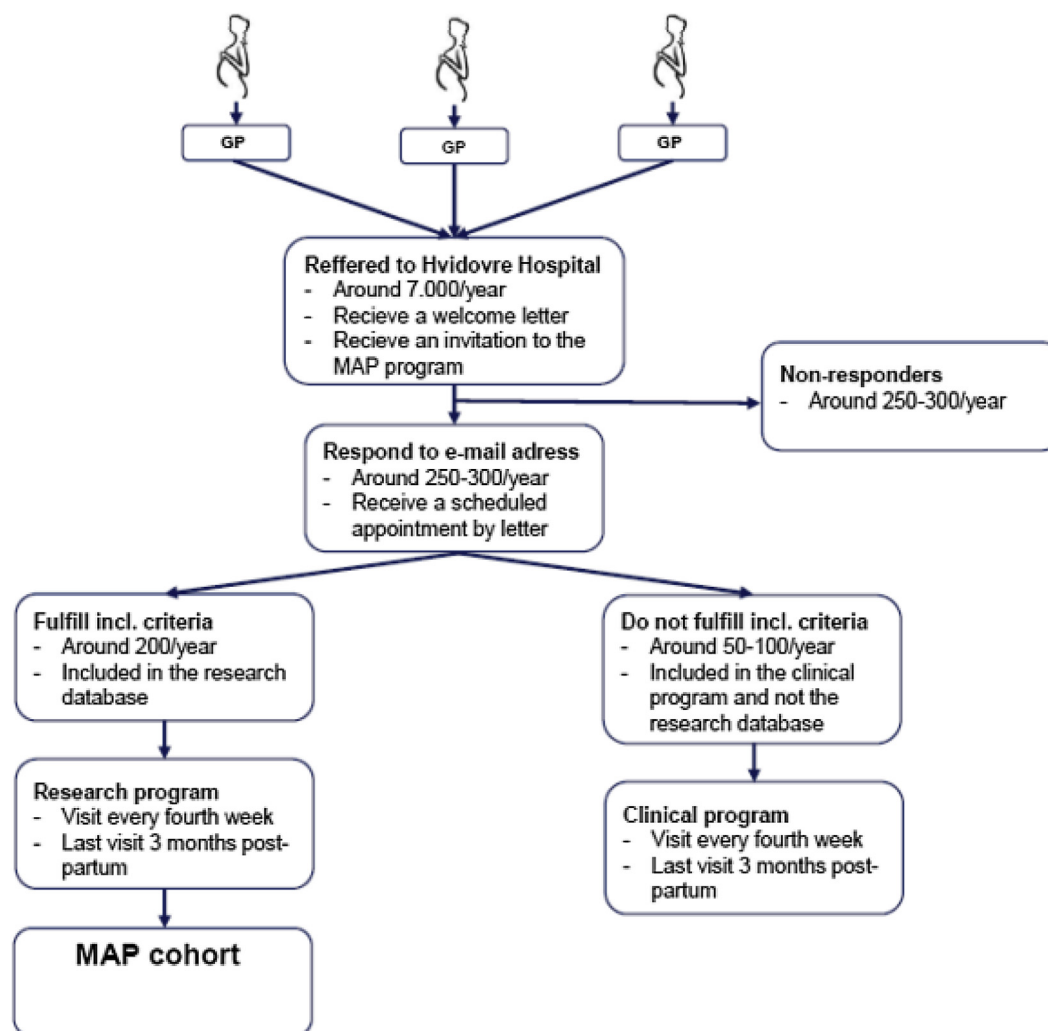


FIG 1. An overview of the MAP cohort. GP, General practitioner.

195 (42%) severe. More than 1 exacerbation was observed in 33 (3%) pregnancies. The mean pre-pregnancy BMI was 24.2 ± 4.5 , first-trimester GWG 5.1 ± 3.4 kg, and total GWG 12.5 ± 5.8 kg (Table I).

Risk factors for exacerbation of asthma during pregnancy

The occurrence of an exacerbation of asthma was related to maternal age, nulliparity, BMI, and both total and first-trimester GWG. The association remained significant after adjusting for level of lung function, smoking status, level of asthma therapy, pre-pregnancy exacerbations, asthma severity, and allergy (Table II).

The impact of first-trimester GWG on the risk of an exacerbation during pregnancy was dose-dependent, with a low risk in women with a GWG of less than 5 kg and an increasing risk with every additional kilogram weight gain hereafter (Fig 2). A maternal first-trimester weight gain of more than 5 kg and a total GWG of more than 13 kg were both significantly associated with increased risk of an asthma exacerbation (OR, 9.35, 95% CI, 6.39-13.68, and 2.89, 95% CI, 2.18-3.83, respectively; $P < .001$). The impact of first-

trimester GWG was independent of maternal pre-pregnancy BMI. In the multiple regression analysis, both GWG in first trimester (OR, 1.24; 95% CI, 1.17-1.31; $P < .001$) and total GWG (OR, 1.05; 95% CI, 1.01-1.09; $P = .02$) were independent risk factors for any exacerbation of asthma during pregnancy (Table III).

Risk factors for severe exacerbations of asthma during pregnancy

The risk of a severe exacerbation was also related to both GWG in first trimester of pregnancy and total GWG independent of the level of lung function, smoking status, level of asthma therapy, level of asthma severity, previous exacerbations, and allergy. Women with a severe exacerbation gained 8 kg in the first trimester compared with 4 kg in women without a severe exacerbation. Correspondingly, the total weight gain was 15 kg compared with 12 kg in women not experiencing a severe exacerbation.

In a further multiple logistic regression analysis (Table III), GWG in first trimester (OR, 1.26; 95% CI, 1.19-1.34; $P \leq .001$) was found also to be a significant risk factor for a severe exacerbation during pregnancy.

TABLE I. Baseline characteristics of 1283 pregnancies in women with asthma enrolled in the MAP program

Characteristics	Pregnancies (1283)
Age (y)	31 ± 5 (17-44)
Allergy	410 (32)
Singleton pregnancies	1247 (97)
Gemelli	36 (3)
Parity	
Para 0	870 (67.8)
Para 1	322 (25.1)
Para 2	71 (5.5)
Para 3	14 (1.1)
Para 4	3 (0.2)
Para 5	3 (0.2)
Sex of fetus (male)	635 (49)
Pre-pregnancy self-reported data	
Weight (kg)	67.8 ± 13.7 (39-204)
BMI (kg/m ²)	24.2 ± 4.5 (15-63)
Underweight (BMI < 18.5)	52 (4)
Normal weight (18.5 ≤ BMI < 25)	822 (64)
Overweight (25 ≤ BMI < 30)	271 (21)
Obese (BMI ≥ 30)	138 (11)
GWG in the first trimester (kg)	5.1 ± 3.4
Measurements at visit 1	
Weight (kg)	72.7 ± 14.7 (41-226)
BMI (kg/m ²)	25.8 ± 4.6 (15-65)
Underweight (BMI < 18.5)	12 (1)
Normal weight (18.5 ≤ BMI < 25)	634 (49)
Overweight (25 ≤ BMI < 30)	434 (34)
Obese (BMI ≥ 30)	203 (16)
Total GWG (kg)	12.5 ± 5.8
Smoking status	
Never smoker	947 (74)
Ever smoker	336 (26)
Current smoker	58 (5)
FEV ₁ < 80% predicted	198 (15)
FEV ₁ ≥ 80% predicted	1085 (85)
Treatment	
Rescue bronchodilator only	472 (37)
Prescribed ICS treatment	811 (63)
Daily dose*	
Low	175 (14)
Medium	434 (34)
High	202 (16)
Oral corticosteroids	1 (0)
Long-acting beta-2 agonist	83 (6)
Leukotriene receptor antagonist	14 (1)
Asthma severity	
Mild asthma	1022 (80)
Severe asthma	261 (20)
Asthma control	
Well-controlled asthma	1066 (83)
Uncontrolled asthma	217 (17)
Pre-pregnancy history of exacerbations	379 (30)
Pre-pregnancy hospitalization due to exacerbations	214 (17)

Data are given as mean ± SD with range in parentheses or numbers with percentages in parentheses.

*Beclometasone equivalent doses.

Postpartum exacerbations of asthma

Approximately 80% (n = 1040) of the cohort was included in postpartum analyses. A postpartum weight loss of less than 50% of total GWG within the first 3 months after delivery was associated with increased risk of a postpartum exacerbation of asthma compared with a greater weight reduction (8% [n = 11] vs

3% [n = 24]; OR, 3.18; 95% CI, 1.51-6.64; *P* = .003). The effect of weight loss remained significant after adjustments for smoking status, ICS treatment, FEV₁ of less than 80% predicted, asthma severity, asthma control, and allergy (OR, 3.29; 95% CI, 1.54-7.04; *P* = .002). Furthermore, the effect of weight loss remained significant after adjusting for exacerbations during pregnancy.

Repeating the multiple logistic regression analysis after exclusion of all women contributing with more than 1 pregnancy throughout the study period did not change the overall results, nor did exclusion of twin pregnancies.

DISCUSSION

This study showed that both excessive weight gain in the first trimester and excessive total GWG are important risk factors for exacerbation of asthma during pregnancy. Further analyses also revealed a direct dose-response relationship between GWG in the first trimester and the risk of an asthma exacerbation during pregnancy.

The cutoff level of excessive GWG associated with increased risk of an exacerbation of asthma during pregnancy was 5 kg in the first trimester and independent of pre-pregnancy BMI. Excessive GWG is common and is observed in nearly 50% of pregnancies.¹⁷ Women with excessive gestational weight gain in the first trimester have a higher risk of maternal and neonatal complication than do women with less weight gain.¹⁸⁻²⁰ A relationship between GWG and maternal asthma control has not been described previously. In contrast, in a prospective cohort study of 146 women, Murphy et al²¹ have shown that women with severe exacerbations of asthma during pregnancy gained significantly less weight than did women without severe exacerbations (*P* = .039). This contradicts the results in the present study, but the differences may be explained by differences in population characteristics and sample size, and possibly by different methods of defining GWG. However, in line with Murphy et al,²¹ we found that nulliparity was associated with a low risk of asthma exacerbations during pregnancy, supporting a relationship between asthma manifestation and parity. This may reflect better asthma control in nulliparous women possibly due to higher health priority.

We also found that a substantial weight reduction postpartum is associated with low risk of a postpartum exacerbation. This corresponds to studies finding that weight loss in obese patients with asthma is associated with more than 50% remission of asthma symptoms, improvement in asthma control, together with an increase in lung function.²² Our findings of an increased risk of an exacerbation depending on GWG or postpartum weight retention suggest a link between fat mass, systemic inflammation, and asthma.

The present study has both important strengths and limitations. Data obtained from the MAP program provide a unique opportunity to investigate the effect of GWG on maternal asthma in a large prospective cohort. All pregnant women with asthma were seen by the same pulmonologist (C.S.U.) at all visits. Maternal weight was measured at each 4-weekly visit, but the maternal pre-pregnancy weight was self-reported. Self-reported pre-pregnancy weight may be lower than actual weight in overweight and obese women, which may underestimate the effect of pre-pregnancy BMI and overestimate the effect of the first-trimester GWG on exacerbations of asthma. Furthermore,

TABLE II. Comparison of characteristics between pregnancies complicated by exacerbation vs no exacerbation (upper panel) and severe exacerbation vs no severe exacerbation (lower panel) in 1283 pregnancies enrolled in the MAP program

Characteristic	Exacerbation (n = 252)	No exacerbation (n = 1031)	OR _{crude} (95% CI)	OR _{adj} (95% CI)	P value
Maternal age (y)	31.8 (4.7)	30.9 (4.8)	1.04 (1.01-1.07)	1.05 (1.02-1.08)	.003
Sex (male)	130 (51.6)	512 (49.7)	0.87 (0.65-1.16)	1.09 (0.80-1.48)	.57
Sex (female)	110 (43.7)	495 (48.0)			
Nulliparous	138 (54.8)	734 (71.2)	0.49 (0.37-0.65)	0.59 (0.44-0.81)	<.001
Multiparous	114 (45.2)	297 (28.8)			
Singleton	240 (95.2)	1007 (97.7)	2.10 (1.03-4.25)	1.50 (0.70-3.20)	.29
Gemelli	12 (4.8)	24 (2.3)			
Pre-pregnancy BMI (kg/m ²)	23.7 (4.2)	24.3 (4.5)	0.97 (0.94-1.00)	0.96 (0.93-0.99)	.04
GWG in the first trimester (kg)	7.3 (3.5)	4.1 (3.4)	1.27 (1.22-1.32)	1.22 (1.17-1.28)	<.001
Total GWG (kg)	14.8 (4.6)	11.6 (5.7)	1.13 (1.09-1.17)	1.13 (1.09-1.17)	<.001

Characteristic	Severe exacerbation (n = 99)	No severe exacerbation (n = 1184)	OR _{crude} (95% CI)	OR _{adj} (95% CI)	P value
Maternal age (y)	32.1 (5.2)	31.0 (4.7)	1.05 (1.00-1.09)	1.05 (1.00-1.10)	.02
Sex (male)	54 (54.5)	588 (49.7)	0.76 (0.49-1.17)	1.25 (0.79-1.99)	.33
Sex (female)	40 (40.4)	565 (47.7)			
Nulliparous	48 (48.5)	824 (69.6)	0.41 (0.27-0.62)	0.51 (0.33-0.78)	.002
Multiparous	51 (51.5)	360 (30.4)			
Singleton	95 (96.0)	1152 (97.3)	1.52 (0.53-4.38)	0.94 (0.31-2.87)	.91
Gemelli	4 (4.0)	32 (2.7)			
Pre-pregnancy BMI (kg/m ²)	24.1 (4.6)	24.2 (4.5)	0.99 (0.95-1.04)	0.99 (0.94-1.04)	.67
GWG in the first trimester (kg)	8.0 (3.6)	4.4 (3.5)	1.25 (1.19-1.32)	1.20 (1.13-1.27)	<.001
Total GWG (kg)	15.3 (4.7)	12.0 (5.7)	1.13 (1.08-1.18)	1.11 (1.06-1.17)	<.001

Data are given as mean $\pm$ SD or numbers with column percentages in parentheses. Results are reported as crude OR with 95% CI and adjusted (adj) OR with 95% CI and *P* value. The OR for the continuous variables represent the increased risk of asthma exacerbation for each kilogram increase in weight and for each year increase in age. The association is adjusted (adj) for smoking status (never smoker vs ever smoker), treatment with ICSs, FEV₁ of less than 80% predicted, pre-pregnancy asthma exacerbations, asthma severity, and allergy. Sex is given only for singleton pregnancies.

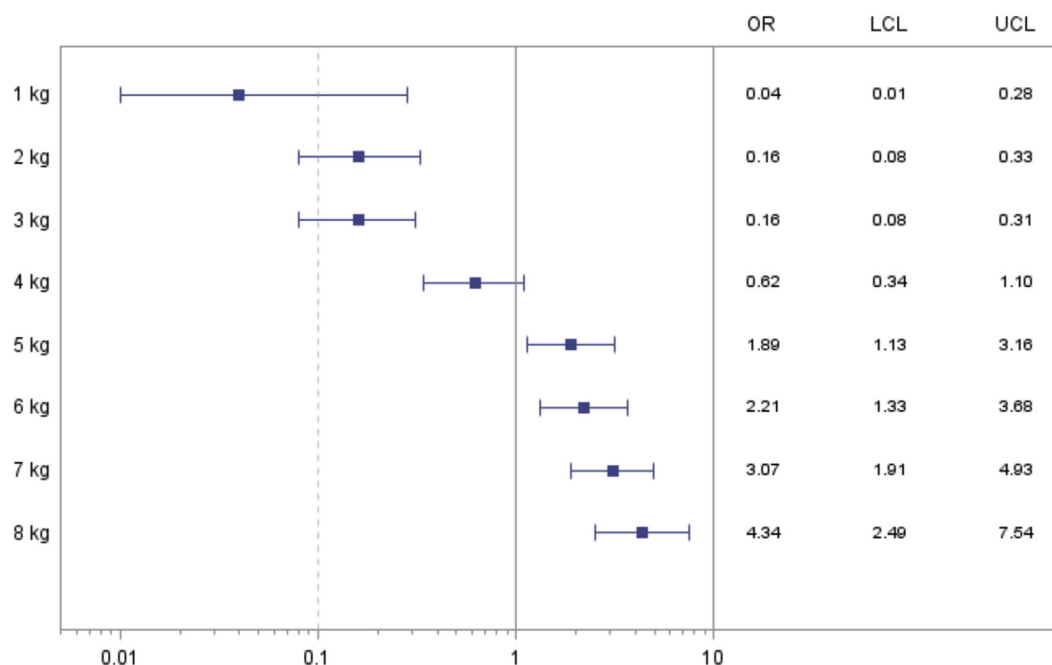


FIG 2. Risk of an exacerbation of asthma according to different cutoff points of GWG in the first trimester of pregnancy. Results are presented as adjusted OR* with lower confidence limits and upper confidence limits. *Adjusted for smoking status (never smoker vs ever smoker), maintenance therapy with inhaled corticosteroid, FEV₁ < 80% predicted, nulliparous, pre-pregnancy asthma exacerbations, asthma severity, and allergy. The reference category is women gaining less than the stated weight gain.

TABLE III. Multiple logistic regression analysis* of risk factors for any exacerbation and severe exacerbations of asthma during pregnancy in 1283 pregnancies enrolled in the MAP program

Risk factors for any exacerbation of asthma during pregnancy			
Risk factor	OR	95% CI	P value
GWG in the first trimester	1.24	1.17-1.31	<.001
Total GWG	1.05	1.01-1.09	.02
Pre-pregnancy BMI	0.96	0.91-1.00	.04
Nulliparous	0.50	0.35-0.70	<.001

Risk factors for severe exacerbation(s) of asthma			
Risk factor	OR	95% CI	P value
GWG in the first trimester	1.26	1.19-1.34	<.001
Nulliparous	0.45	0.27-0.74	.002

Results are given as OR with 95% CI and P value. Severe exacerbation defined as an exacerbation requiring hospital admission, emergency department treatment, and/or a rescue course of systemic corticosteroid.

*Multiple logistic regression analysis with stepwise backward elimination.

only approximately 80% of the cohort attended the last scheduled visit before the due date, which may have underestimated the GWG in the cohort. Nevertheless, a systematical underestimation or overestimation of the GWG cannot explain the dose-response effect between first-trimester GWG and the risk of exacerbations.

On the basis of the prevalence of asthma in Denmark,²³ approximately two-third of women with asthma giving birth each year at Hvidovre Hospital are enrolled in the MAP program. The women enrolled in the MAP cohort are comparable to the background population of pregnant women with regard to age and marital status.²⁴ However, as in other population studies, there is a risk of several types of bias including factors associated with lifestyle that are not easily measured. We have earlier found that a higher proportion of nulliparous women accept an invitation to participate in a lifestyle interventional trial addressing GWG during pregnancy at our department.²⁵ A predominance of nulliparous women was also found in the present study.

Our findings have clinical implications for maternal and child health care. Excessive GWG can be prevented by counseling early in pregnancy and by raising public awareness.²⁶ Health care providers should advise pregnant women about the importance of a healthy rate of GWG, especially during the first trimester of pregnancy, to help them gain the recommended amount of weight during pregnancy. Future studies should investigate whether interventions to reduce excessive GWG in the first trimester may reduce the risk of maternal exacerbations of asthma and thus prevent potential complications associated with exacerbations of asthma during pregnancy.

Conclusions

In a large cohort of 1283 pregnancies, we found that excessive GWG in the first trimester and total GWG are associated with increased risk of asthma exacerbations during pregnancy. GWG more than 5 kg in the first trimester was associated with increased risk of an exacerbation.

Our findings highlight the importance of advising pregnant women on GWG (the importance of GWG in first trimester should

be emphasized), to prevent possible asthma-related pregnancy complications.

Clinical implications: Excessive gestational weight gain is a risk factor for exacerbations of asthma during pregnancy and a healthy rate of gestational weight gain may improve the outcome in mother and child.

REFERENCES

- Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61:169-76.
- Enriquez R, Griffin MR, Carroll KN, Wu P, Cooper WO, Gebretsadik T, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;120:625-30.
- Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol* 1988;81:509-17.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2017. Available at: www.ginasthma.org. Accessed May 8, 2017.
- von Ruesten A, Steffen A, Floegel A, van der AD, Masala G, Tjønneland A, et al. Trend in obesity prevalence in European adult cohort populations during follow-up since 1996 and their predictions to 2015. *PLoS One* 2011;6:e27455.
- Helms E, Coulson CC, Galvin SL. Trends in weight gain during pregnancy: a population study across 16 years in North Carolina. *Am J Obstet Gynecol* 2006;194:e32-4.
- Hendler I, Schatz M, Momirova V, Wise R, Landon M, Mabie W, et al. Association of obesity with pulmonary and nonpulmonary complications of pregnancy in asthmatic women. *Obstet Gynecol* 2006;108:77-82.
- Harskamp-van Ginkel MW, London SJ, Magnus MC, Gademan MG, Vrijkotte TG. A study on mediation by offspring BMI in the association between maternal obesity and child respiratory outcomes in the Amsterdam Born and Their Development Study Cohort. *PLoS One* 2015;10:e0140641.
- Ferretti G, Cester AM, Bacchetti T, Raffaelli F, Vignini A, Orici F, et al. Leptin and paraoxonase activity in cord blood from obese mothers. *J Matern Fetal Neonatal Med* 2014;27:1353-6.
- Halonen M, Lohman IC, Stern DA, Ellis WL, Rothers J, Wright AL. Perinatal tumor necrosis factor- α production, influenced by maternal pregnancy weight gain, predicts childhood asthma. *Am J Respir Crit Care Med* 2013;188:35-41.
- Forno E, Young OM, Kumar R, Simhan H, Cledon JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. *Pediatrics* 2014;134:e535-46.
- Ferraro ZM, Qiu Q, Gruslin A, Adamo KB. Excessive gestational weight gain and obesity contribute to altered expression of maternal insulin-like growth factor binding protein-3. *Int J Womens Health* 2013;5:657-65.
- Karakosta P, Georgiou V, Fthenou E, Papadopoulou E, Roumeliotaki T, Margioris A, et al. Maternal weight status, cord blood leptin and fetal growth: a prospective mother-child cohort study (Rhea study). *Paediatr Perinat Epidemiol* 2013;27:461-71.
- Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011;378:983-90.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
- Wells CS, Schwalberg R, Noonan G, Gabor V. Factors influencing inadequate and excessive weight gain in pregnancy: Colorado, 2000-2002. *Matern Child Health J* 2006;10:55-62.
- Kowal C, Kuk J, Tamim H. Characteristics of weight gain in pregnancy among Canadian women. *Matern Child Health J* 2012;16:668-76.
- Johnson JL, Farr SL, Dietz PM, Sharma AJ, Barfield WD, Robbins CL. Trends in gestational weight gain: the Pregnancy Risk Assessment Monitoring System, 2000-2009. *Am J Obstet Gynecol* 2015;212:806.e1-8.
- Hantoushzadeh S, Sheikh M, Bosaghzadeh Z, Ghotbizadeh F, Tarafdari A, Panahi Z, et al. The impact of gestational weight gain in different trimesters of pregnancy on glucose challenge test and gestational diabetes. *Postgrad Med J* 2016;92:502-4.
- Liu Z, Ao D, Yang H, Wang Y. Gestational weight gain and risk of gestational diabetes mellitus among Chinese women. *Chin Med J (Engl)* 2014;127:1255-60.

21. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005;106:1046-54.
22. Juel CT, Ali Z, Nilas L, Ulrik CS. Asthma and obesity: does weight loss improve asthma control? A systematic review. *J Asthma Allergy* 2012;5:21-6.
23. Thomsen SF, Ulrik CS, Larsen K, Backer V. Change in prevalence of asthma in Danish children and adolescents. *Ann Allergy Asthma Immunol* 2004;92:506-11.
24. Ali Z, Nilas L, Ulrik CS. Low risk of adverse obstetrical and perinatal outcome in pregnancies complicated by asthma: a case control study. *Respir Med* 2016;120:124-30.
25. Gesche J, Renault K, Norgaard K, Nilas L. Representativeness of participants in a lifestyle intervention study in obese pregnant women—the difference between study participants and non-participants. *Obes Facts* 2014;7:351-60.
26. Liu J, Wilcox S, Whitaker K, Blake C, Addy C. Preventing excessive weight gain during pregnancy and promoting postpartum weight loss: a pilot lifestyle intervention for overweight and obese African American women. *Matern Child Health J* 2015;19:840-9.