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Original Article

Factors Associated with Asthma Exacerbations During Pregnancy

Marleen P. Bokern, MSc[a], Annelies L. Robijn, PhD[b], Megan E. Jensen, PhD[b], Daniel Barker, PhD[c], Leonie Callaway, PhD[d,e], Vicki Clifton, PhD[f], Peter Wark, PhD[g,h], Warwick Giles, PhD[c], Joerg Mattes, PhD[b,i], Michael Peek, PhD[j], John Attia, PhD[c], Sean Seeho, PhD[k], Alistair Abbott, MBBS[l,m], Peter G. Gibson, DMed[g,h], and Vanessa E. Murphy, PhD[b] *Groningen, The Netherlands; and Newcastle and Sydney, New South Wales; and South Brisbane and Herston, Queensland, Australia*

What is already known about this topic? Up to 45% of women experience an asthma exacerbation during pregnancy that is associated with adverse pregnancy outcomes.

What does this article add to our knowledge? A history of asthma exacerbations and poor asthma control despite treatment with moderate-to high-dose inhaled corticosteroids or long-acting β-agonists predict severe asthma exacerbations during pregnancy.

How does this study impact current management guidelines? Identifying a history of exacerbation and poor asthma symptom control as measured by the Asthma Control Questionnaire, despite treatment with inhaled corticosteroids or long-acting β-agonists identifies those at high risk for exacerbation during pregnancy. Factors associated with asthma exacerbations during pregnancy may help health care professionals optimize asthma management during pregnancy.

BACKGROUND: Asthma exacerbations during pregnancy are associated with adverse pregnancy outcomes.
OBJECTIVE: The aim of this study was to establish factors associated with asthma exacerbations during pregnancy.
METHODS: We obtained data from three cohorts of pregnant women with asthma recruited in eastern Australia (2004-2019; n = 1461). Severe exacerbations were defined as episodes of asthma requiring hospitalization, an emergency department visit, or prescription of oral corticosteroids after enrollment. Baseline information on potential risk factors included demographic characteristics, asthma characteristics (eg, lung function, asthma triggers, asthma control, medication use), pregnancy factors (eg, fetal sex, parity, antenatal care type), and other maternal factors (body mass index, smoking status, mental health). Backward stepwise logistic regression and Akaike information criterion were used to determine the best-fitting model.

[a]Department of Pharmaco-Therapy, Epidemiology, and Economics, University of Groningen, Groningen, The Netherlands
[b]Priority Research Centre GrowUpWell, School of Medicine and Public Health, University of Newcastle, Hunter Medical Research Institute, Newcastle, New South Wales, Australia
[c]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia
[d]Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia
[e]Women's and Newborn Services, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia
[f]Mater Research Institute, University of Queensland, Translational Research Institute, South Brisbane, Queensland, Australia
[g]Priority Research Centre for Healthy Lungs, School of Medicine and Public Health, University of Newcastle, Hunter Medical Research Institute, Newcastle, New South Wales, Australia
[h]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia
[i]Pediatric Respiratory and Sleep Medicine Department, John Hunter Children's Hospital, Newcastle, New South Wales, Australia
[j]ANU Medical School, College of Health and Medicine, The Australian National University, Garran, Australian Capital Territory, Australia
[k]Department of Obstetrics and Gynaecology, Sydney Medical School Northern, University of Sydney, Royal North Shore Hospital, St Leonards, Sydney, New South Wales, Australia
[l]Department of Respiratory and Sleep Medicine, Nepean Hospital, Kingswood, New South Wales, Australia
[m]Nepean Clinical School, University of Sydney, Sydney, New South Wales, Australia

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Corresponding author: Vanessa E. Murphy, PhD, Level 2 West Wing, Hunter Medical Research Institute, University of Newcastle, Lot 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. E-mail: Vanessa.Murphy@newcastle.edu.au.
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Abbreviations used
ACQ- Asthma Control Questionnaire
AIC- Akaike information criterion
AP II- Phase II Asthma in Pregnancy study
AUC- Area under the curve
BDP- Beclomethasone dipropionate
BLT- Breathing for Life Trial
BMI- Body mass index
EPDS- Edinburgh Postnatal Depression Scale
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
LABA- Long-acting β-agonist
MAP- Management of Asthma in Pregnancy
OCS- Oral corticosteroid
RCT- Randomized controlled trial
VEAP- Viral Exacerbations of Asthma in Pregnancy

RESULTS: A total of 135 participants experienced a severe exacerbation during pregnancy (9.2%). Medium to high ICS dose was most strongly associated with severe asthma exacerbations (adjusted odds ratio = 3.20; 95% confidence interval, 1.85-5.53). Worse asthma control, possession of a written action plan, and a history of asthma exacerbations in the year preceding pregnancy were associated with an increased rate of exacerbations.

CONCLUSIONS: Asthma exacerbations before pregnancy and more severe asthma at the beginning of pregnancy were associated with an increased rate of exacerbations during pregnancy. Despite Global Initiative for Asthma step 3 and 4 treatment and optimal management including a written asthma action plan, there is still a significant asthma burden in a group of women at high risk for severe exacerbations in pregnancy. **(J Allergy Clin Immunol Pract 2021;9:4343-52)**

Key words: *Asthma; Pregnancy; Exacerbation; Risk factors*

INTRODUCTION

The prevalence of asthma among pregnant women in the United States is around 8%,[1,2] which makes it the most common chronic illness in pregnancy.[3,4] It is important to monitor asthma during pregnancy because 20% to 45% of women experience exacerbations requiring medical intervention during pregnancy.[4,5] Poorly controlled maternal asthma and exacerbations are associated with poor pregnancy outcomes, including lower birth weight,[6-8] preterm birth,[6,9] preeclampsia,[6,7,10] spontaneous abortion,[11] and congenital malformations.[12,13] Poorly controlled asthma is also associated with an increased risk for perinatal mortality and childhood asthma.[13-15]

Increased asthma severity before pregnancy has been associated with an increased risk for exacerbations during pregnancy.[5,16,17] Schatz et al[5] found that patients whose asthma was classified as mild were significantly less likely to have an exacerbation (12.6%) compared with patients with moderate (25.7%) or severe asthma (51.9%). Murphy et al[12] also found that asthma severity was associated with an increased incidence of exacerbations during pregnancy. A Danish study developed a prediction model to identify pregnant women at low risk for exacerbations and found that clinically stable asthma at the beginning of the study (odds ratio [OR] = 0.28; 95% confidence interval [CI], 0.18-0.42), along with no history of previous exacerbations (OR = 0.22; 95% CI, 0.14-0.35) and no prescribed controller medication (OR = 0.05; 95% CI, 0.02-0.15), were associated with low risk for exacerbations.[18]

Other previously identified risk factors for asthma exacerbations during pregnancy include smoking,[19] respiratory viral infections,[12] rhinitis,[20,21] anxiety,[22] obesity,[23,24] and excessive gestational weight gain.[25] Factors that have been associated with an increased risk for recurrent uncontrolled asthma during pregnancy include inhaled corticosteroid (ICS) use at the beginning of pregnancy and increasing maternal age.[26] Being pregnant with a female fetus has been suggested to be a potential risk factor for exacerbations,[1,27,28] but this has not been confirmed by other studies.[29,30]

Considering the potentially severe consequences of asthma exacerbations during pregnancy, it is important for women to receive optimal advice and the best possible treatment for asthma. Many previous studies were conducted in a relatively small number of patients and assessed only single risk factors. The aim of our study was to determine patient- and asthma-related factors associated with asthma exacerbations during pregnancy in a large, well-described cohort.

METHODS

Data for this study came from the Asthma and Pregnancy Phase II Study (AP II),[19] the Managing Asthma in Pregnancy (MAP) study,[31] the Viral Exacerbations of Asthma in Pregnancy (VEAP) study,[32] and the Breathing for Life Trial (BLT),[33] all studies on asthma during pregnancy conducted across eastern Australia using similar methodology; most participants were recruited in Newcastle. All women were aged 18 years or older with physician-diagnosed asthma. Baseline data were collected before 23 weeks' gestation. We excluded participants who withdrew from the study owing to miscarriage (<20 weeks). The AP II was a cohort study conducted at the John Hunter Hospital between 2004 and 2006 (n = 84).[19] The MAP and VEAP studies (n = 280) were conducted between 2007 and 2010. The MAP study was a double-blind, parallel group, randomized controlled trial (RCT) (n = 220) that assessed the effect of FeNO-based asthma management compared with symptom-based asthma management in nonsmokers. In addition, women who smoked (n = 49) were randomized to treatment adjustment according to symptoms or FeNO in a pilot RCT according to the MAP protocol. A further 11 women participated in an observational study of VEAP. These women were not randomized to an intervention group but underwent the same clinical assessments as those in the MAP study. Finally, BLT was a parallel-group RCT (n = 1200) recruited between 2013 and 2019, which compared FeNO-based asthma management with usual care. Only women for whom outcome data were available at the time of this analysis were included (n = 1097). Additional information about the cohorts is listed in Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

Variables obtained for analysis included the study cohort, demographic characteristics (maternal age and ethnicity), asthma characteristics (baseline lung function, self-reported asthma triggers, asthma control [assessed using the Asthma Control Questionnaire (ACQ)[34] and Global Initiative for Asthma (GINA) assessment of asthma[35]], exacerbation history, baseline use of ICS and long-acting β-agonists [LABA], asthma management education, inhaler technique, possession of a written action plan (WAP), and, where

applicable, dose of ICS and medication adherence), factors relating to the pregnancy (fetal sex, parity, multiple pregnancy, antenatal care type, and gestational age at study recruitment), and other factors related to maternal health (body mass index [BMI], smoking status, and Edinburgh Postnatal Depression Scale [EPDS] score at first antenatal visit). FeNO and ACQ score were not measured in women randomized to the control arm of BLT. Model of care was classified as midwife-led, medical, or shared care (in which a general practitioner was the primary carer) based on what was reported in the medical records at birth (see the Appendix in this article's Online Repository at www.jaci-inpractice.org). Edinburgh Postnatal Depression Scale scores of 9 or lower were classified as low, 10 to 12 as medium, and 13 or greater as high.[36] Edinburgh Postnatal Depression Scale score and model of care were available only for patients from the Hunter New England Health District (John Hunter Hospital, Newcastle, New South Wales and Maitland Hospital, Maitland, New South Wales). Participants were classified as non-overweight if the early pregnancy BMI was less than 25 kg/m^2, overweight if the BMI was 25 to 30 kg/m^2, and obese if the BMI was greater than 30 kg/m^2.[37] Inhaler technique was assessed by a nurse as optimal or adequate versus inadequate.[38] Technique of two types of inhalers were combined into one variable (inhaler technique).

At baseline, spirometry was performed[39] and airway obstruction was defined as FEV_1/FVC less than 70%. Asthma self-management skills were assessed and optimized when necessary, as described elsewhere.[39] Recent asthma history was self-reported as the number of hospitalizations, emergency department visits, or OCS courses in the past year, and dichotomous as any or none. Information on current asthma medication use was self-reported. If a woman reported missing more than 20% of ICS doses in the 2 weeks preceding recruitment, she was classified as nonadherent.[38,39] Dose of prescribed ICS was categorized into low or medium to high based on cutoff values reported in the 2020 GINA guidelines: low ICS dose was defined as 1 to 500 μg beclomethasone dipropionate (BDP) equivalents per day, and medium to high dose was greater than 500 μg BDP equivalents per day.[35]

Ethnicity was recorded at baseline; answers were regrouped as White/European, Aboriginal/Torres Strait Islander (Indigenous Australians), and other/unknown (see the Appendix). Smoking status and asthma triggers were self-reported at baseline. Triggers were classed into nine categories: season, reflux, exercise, upper respiratory tract infection, work, pets, food, aspirin, and fumes.

Outcome definition

Severe exacerbations were defined as worsening of asthma requiring hospitalization, emergency department presentation, or a course of OCS.[33,40] Prescription of a course of OCS for an asthma exacerbation was separately assessed as an outcome. Only exacerbations that occurred after enrollment were included. In the AP II, MAP, and VEAP cohorts, exacerbation data were recorded prospectively during study visits and checked against medical records. In BLT, exacerbations were recorded during a postpartum telephone interview and verified by review of hospital medical records when possible.[33]

Statistical analysis

We conducted statistical analysis using IBM SPSS Statistics for Windows (version 26, Armonk, NY: IBM Corp). Distribution of covariates between women with and without exacerbations was assessed using chi-square test for categorical variables, Student *t* test for normally distributed continuous variables, and Mann-Whitney test for nonnormally distributed variables. The statistical significance threshold was set to P less than .05.

We conducted backward stepwise logistic regression analysis. Variables with P less than .2 in the baseline analysis were included in the model selection. Only women with complete data for all variables in the initial model were included. Variables were excluded stepwise based on the highest P value above .05 until the best-fitting model was identified using Akaike information criterion (AIC). The model with the lowest AIC was then applied to the entire dataset and the area under the curve (AUC) was calculated. we used the Hosmer-Lemeshow test to assess the model fit.

In the initial model selection, we excluded the EPDS score and model of care because of the high proportion of missing values and included them in a sensitivity analysis. Furthermore, omission of food as a trigger from model selection was performed as a sensitivity analysis owing to the lack of detail. To increase the clinical utility of the resulting models, EPDS score and BMI were considered to be categorical variables, with the categories determined by routinely used cutoff scores.

RESULTS

The dataset included 1461 women: 84 from the AP II study (5.7%), 280 from the MAP/VEAP cohorts (19.2%), and 1097 from BLT (75.1%). Of all 1491 participants, 135 experienced at least one severe asthma exacerbation during pregnancy (9.2%; 13.1% from the AP II study, 9.6% from MAP/VEAP, and 8.8% from BLT) (Table I).

Baseline asthma control was significantly worse in women who later experienced an exacerbation ($P = .001$ as assessed by ACQ and $P < .001$ as assessed by GINA). Asthma exacerbations before pregnancy were associated with more exacerbations during pregnancy ($P < .001$). Women with good inhaler technique and a WAP for asthma more frequently experienced exacerbations ($P = .016$ and $P < .001$, respectively). Women who used higher doses of ICS (>500 μg/d) were more likely to have an exacerbation than were women who did not use ICS or used lower doses ($P < .001$). Three-quarters of women receiving medium to high doses were receiving ICS or LABA therapy.

A total of 99 women received a course of OCS for asthma during pregnancy (6.8%; 10.7% from AP II, 8.6% from MAP/VEAP, and 6.0% from BLT). Patients who received a course of OCS had significantly lower FEV_1 (% predicted) ($P = .046$) and FVC (% predicted) ($P = .024$) at baseline compared with patients who did not receive OCS. Use of higher doses of ICS (>500 μg BDP at baseline) were associated with more frequent use of OCS compared with no use of ICS ($P < .001$) or use of lower doses ($P < .001$). As with the outcome of severe exacerbation, baseline asthma symptoms, assessed using either ACQ or GINA, were significantly higher in patients who received OCS ($P = .001$ and $P < .001$, respectively). Increased EPDS score at baseline was associated with more frequent OCS prescription ($P = .001$).

Model selection

We used only the combined asthma history variable because of collinearity among individual asthma history variables. Of the spirometry variables, only FEV_1 (%) was used in the model selection. The ACQ score had a high percentage of missing values (37%) and showed collinearity with the GINA assessment of

TABLE I. Baseline characteristics of study participants with and without exacerbations

Variable	No severe exacerbation (n = 1326) (90.8%)	Severe exacerbation (n = 135) (9.2%)	*P*	No oral corticosteroid course (n = 1362) (93.2%)	Oral corticosteroid course (n = 99) (6.8%)	*P*
Age, y (mean [SD])	29.8 (5.5)	30.1 (5.7)	.628	29.8 (5.5)	30.2 (5.3)	.524
Ethnicity			.964			.718
White/European	1044 (78.7%)	105 (77.8%)		1073 (78.8%)	76 (76.8%)	
Aboriginal/Torres Strait Islander	64 (4.8%)	7 (5.2%)		67 (4.9%)	4 (4.0%)	
Other/unknown	218 (16.4%)	23 (17.0%)		222 (16.3%)	19 (19.2%)	
Fetal sex: male (%)	628/1282 (49.0 %)	74/130 (56.9%)	.085	650/1315 (49.4%)	52/97 (53.6%)	.427
Multiple pregnancy	31/1316 (2.4%)	5 (3.7%)	.338	34/1352 (2.5%)	2 (2.0%)	.760
Multiparity	664/1312 (50.6%)	87/133 (64.4%)	**.002**	685/1348 (50.8%)	66 (66.7%)	**.002**
Body mass index, kg/m^2 (median [IQR])	27.5/1293 (24.0; 32.9)	28.6/133 (24.9; 34.3)	.109	27.56/1329 (24.02; 32.96)	27.93/97 (24.59; 33.51)	.517
Body mass index category						
Not overweight	416/1293 (32.2%)	34/133 (25.6%)	.079	424/1329 (31.9%)	26/97 (26.8%)	.302
Overweight	399/1293 (30.9%)	41/133 (30.8%)		409/1329 (30.8%)	31/97 (32.0%)	
Obese	478/1293 (37.0%)	58/133 (43.6%)		496/1329 (37.3%)	40/97 (41.2%)	
Edinburgh Postnatal Depression Scale score (median [IQR])	5 (2; 9) n = 803	7 (4; 12) (n = 93)	**.001**	5 (2; 9) (n = 827)	8 (4; 12) (n = 69)	**.001**
Edinburgh Postnatal Depression Scale score category						
Low (≤9)	632/803 (78.7%)	62/93 (66.7%)	**.008**	649/827 (78.5%)	45/69 (65.2%)	**.011**
Medium (10-12)	101/803 (12.6%)	17/93 (18.3%)		105/827 (12.7%)	13/69 (18.8%)	
High (≥13)	70/803 (8.7%)	14/93 (15.1%)		73/827 (8.8%)	11/69 (15.9%)	
Smoking status			.456			.139
Current smoker	161/1262 (12.8%)	21/126 (16.7%)		165/1297 (12.7%)	17/91 (18.7%)	
Former smoker	398/1262 (31.5%)	37/126 (29.4%)		413/1297 (31.8%)	22/91 (24.2%)	
Never smoker	703/1262 (55.7%)	68/126 (54.0%)		719/1297 (55.4%)	52/91 (57.1%)	
Triggers						
Season	1129/1324 (85.3%)	121 (89.6%)	.169	1163/1360 (85.5%)	87 (87.9%)	.517
Reflux	164/1322 (12.4%)	25 (18.5%)	**.044**	165/1358 (12.2%)	24 (24.2%)	**.001**
Exercise	999/1324 (75.5%)	107 (79.3%)	.325	1030/1360 (75.7%)	76 (76.8%)	.817
Upper respiratory tract infection	1138/1324 (86.0%)	123 (91.1%)	.095	1171/1360 (86.1%)	90 (90.9%)	.178
Work	187/1325 (14.1%)	29 (21.5%)	**.022**	195/1361 (14.3%)	21 (21.2%)	.062
Pet	494/1324 (37.3%)	63 (46.7%)	**.033**	512/1360 (37.6%)	45 (45.5%)	.123
Food	305/1325 (23.0%)	50 (37.0%)	**<.001**	317/1361 (23.3%)	38 (38.4%)	**.001**
Aspirin	39/1325 (2.9%)	11/134 (8.2%)	**.001**	40/1361 (2.9%)	10/98 (10.2%)	**.001**
Fumes	845/1325 (63.8%)	103 (76.3%)	**.004**	875/1361 (64.3%)	73 (73.7%)	.057
Total number of triggers (mean [SD])	4.0 (1.5) (n = 1318)	4.7 (1.7) (n = 134)	**<.001**	4.0 (1.5) (n = 1354)	4.7 (1.8) (n = 98)	**.001**
Spirometry (mean [SD])						
FEV_1 (%)	90.2 (13.5) (n = 1126)	87.6 (16.5) (n = 115)	.102	90.2 (13.5) (n = 1156)	86.4 (17.1) (n = 85)	**.046**
FVC (%)	94.4 (12.5) (n = 1116)	92.1 (14.3) (n = 113)	.070	94.4 (12.5) (n = 1145)	91.2 (14.6) (n = 84)	**.024**
FEV_1/FVC	80.8 (7.5) (n = 1118)	80.2 (11.4) (n = 114)	.617	80.8 (7.6) (n = 1147)	79.8 (12.2) (n = 85)	.273
Obstruction at baseline (FEV_1/FVC < 70%)	100/1118 (8.9%)	13/114 (11.4%)	.386	103/1147 (9.0%)	10/85 (11.8%)	.391
FeNO (median [IQR])	15.8 (9.0; 29.0) (n = 798)	14.0 (8.5; 27.4) (n = 85)	.364	15.7 (9.0; 29.0) (n = 819)	13.6 (9.0; 26.6) (n = 64)	.368

Asthma control						
Asthma Control Questionnaire score (median [IQR])	1.00 (0.43; 1.71) (n = 828)	1.29 (0.86; 2.63) (n = 88)	**.001**	1.00 (0.43; 1.71) (n = 850)	1.43 (0.82; 2.86) (n = 66)	**.001**
Uncontrolled (Asthma Control Questionnaire >1.5)	278/828 (33.6%)	39/88 (44.3%)		285/850 (33.5%)	32/66 (48.5%)	
Global Initiative for Asthma assessment of asthma control			**<.001**			**<.001**
Well-controlled	344/1292 (26.6%)	18/133 (13.5%)		347/1328 (26.1%)	15/97 (15.5%)	
Partly controlled	570/1292 (44.1%)	46/133 (34.6%)		586/1328 (44.1%)	30/97 (30.9%)	
Uncontrolled	378/1292 (29.3%)	69/133 (51.9%)		395/1328 (29.7%)	52/97 (53.6%)	
Asthma history (past 12 mo)						
Hospitalizations (≥1)	41/1304 (3.1%)	14/133 (10.5%)	**<.001**	42/1340 (3.1%)	13/97 (13.4%)	**<.001**
Emergency department visits (≥1)	116/1304 (8.9%)	33/133 (24.8%)	**<.001**	123/1340 (9.2%)	26/97 (26.8%)	**<.001**
Oral corticosteroid courses (≥1)	219/1303 (16.8%)	60/133 (45.1%)	**<.001**	229/1339 (17.1%)	50/97 (51.5%)	**<.001**
Any of the above (≥1)	258/1303 (19.8%)	65/133 (48.9%)	**<.001**	269/1339 (20.1%)	54/97 (55.7%)	**<.001**
Asthma management						
Knowledge of reliever	357/1194 (29.9%)	35/114 (30.7%)	.858	365/1225 (29.8%)	27/83 (32.5%)	.599
Knowledge of controller	170/712 (23.9%)	20/81 (24.7%)	.871	173/726 (23.8%)	17/67 (25.4%)	.777
Written action plan	204/1295 (15.8%)	41/133 (30.8%)	**<.001**	212/1331 (15.9%)	33/97 (34.0%)	**<.001**
Good inhaler technique	331/1160 (28.5%)	41/103 (39.8%)	**.016**	339/1185 (28.6%)	33/78 (42.3%)	**.010**
Use of controller medication						
Missed doses (past 7d) (%)	14.3 (0.0; 42.9) (n = 476)	7.1 (0.0; 35.7) (n = 81)	.560	14.3 (0.0; 42.9) (n = 491)	7.1 (0.0; 42.9) (n = 66)	.970
Nonadherence*	179/476 (37.6%)	32/81 (39.5%)	.744	182/491 (37.1%)	29/66 (43.9%)	.280
Inhaled corticosteroid dose			**<.001**			**<.001**
No use	824/1302 (63.3%)	51/133 (38.3%)		844/1336 (62.0%)	31 (31.3%)	
Low dose (1-500 μg beclomethasone dipropionate)	327/1302 (25.1%)	37/133 (27.8%)		336/1336 (25.1%)	28 (28.3%)	
Medium/high dose (>500 μg beclomethasone dipropionate)	151/1302 (11.6%)	45/133 (33.8%)		156/1336 (11.7%)	40 (40.4%)	
Long-acting β-agonist use	378 (28.5%)	68 (50.4%)	**.001**	391 (28.7%)	55 (55.6%)	**.001**
Model of care			.120			.078
Midwife	430/824 (52.2%)	45/99 (45.5%)		445/850 (52.4%)	30/73 (41.1%)	
Medical	307/824 (37.3%)	47/99 (47.5%)		317/850 (37.3%)	37/73 (50.7%)	
Shared care	87/824 (10.6%)	7/99 (7.1%)		88/850 (10.4%)	6/73 (8.2%)	
Gestational age (wk) at recruitment (mean [SD])	18.4 (3.0)	18.2 (3.2)	.484	18.4 (3.0)	18.1 (3.3)	.273

IQR, interquartile range.
Bold *P* values indicate statistical significance.
*Nonadherent if missed doses in past week equal or more than 20%.

TABLE II. Univariate and multivariate logistic regression of risk factors associated with severe exacerbation

	Unadjusted			Adjusted (n/N* = 95/1173)		
Variable	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Fetal sex: male	1.376	0.956-1.980	.086	1.446	0.920-2.271	.110
Parity: multiparous	1.769	1.223-2.557	.002	1.663	1.043-2.651	.033
Written action plan	2.383	1.602-3.546	<.001	1.796	1.070-3.016	.027
Good inhaler technique	1.656	1.094-2.507	.017	1.433	0.895-2.296	.134
History asthma exacerbation past 12 mo	3.872	2.684-5.584	<.001	2.533	1.583-4.054	<.001
Trigger: food	1.967	1.356-2.854	<.001	1.552	0.969-2.485	.067
Global Initiative for Asthma asthma control			<.001			.028
Well-controlled	Reference			Reference		
Partly controlled	1.542	0.880-2.703	.130	1.406	0.707-2.799	.332
Uncontrolled	3.489	2.035-5.980	<.001	2.290	1.164-4.505	.016
Inhaled corticosteroid use			<.001			<.001
No use	Reference			Reference		
Low dose (1-500 μg beclomethasone dipropionate equivalents)	1.828	1.175-2.845	.007	1.239	0.704-2.183	.458
Medium/high dose (>500 μg beclomethasone dipropionate equivalents)	4.815	3.111-7.452	<.001	3.196	1.848-5.526	<.001

*Number of exacerbations per total sample size.

asthma control; therefore, it was not included in the model selection.

Severe exacerbation model

For the outcome of severe exacerbations, the model including fetal sex, parity, food as a trigger, GINA asthma control, history of asthma exacerbations, inhaler technique, presence of a WAP, and ICS dose had the lowest AIC (Table II and Figure 1, *A*). The AUC was 0.751 (95% CI, 0.695-0.807) (see Figure E1, *A* in this article's Online Repository at www.jaci-inpractice.org). The model selection was conducted including 1005 patients. When EPDS score and model of care were included in the model selection, EPDS score remained in the final model (see Table E2 in this article's Online Repository at www.jaci-inpractice.org), but it was not significant, and the AUC did not increase (AUC = 0.732; 95% CI, 0.668-0.796) (Figure E1, *C*). Model selection was conducted including 587 patients. Omission of food as a trigger did not result in a different model selection (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Oral corticosteroid use model

For the outcome of OCS course, the model including reflux as a trigger, food as a trigger, FEV_1 (%), history of asthma exacerbations, inhaler technique, possession of a WAP, smoking status, and ICS dose was the best model (Table III and Figure 1, *B*) (AUC = 0.768; 95% CI, 0.705-0.832) (see Figure E1, *B*). Model selection included 994 women.

The EPDS score and model of care were not retained in the sensitivity analysis. Omission of food as a trigger did not result in a different model selection (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

For all selected models, the Hosmer-Lemeshow test gave a *P* value greater than .05, indicating satisfactory models.

To investigate whether adequate or optimal inhaler technique and possession of a WAP might be associated with baseline severity of asthma, we determined associations with ICS dose and history of exacerbation. More women with a WAP were receiving medium-to high-dose ICS compared with women without a WAP (23% vs 12%; $P < .001$), and a larger proportion had a history of exacerbation (42% vs 19%; $P < .001$). More women with adequate or optimal inhaler technique were receiving medium-to high-dose ICS (21% vs 11%; $P < .001$); however, no there was no difference in exacerbation history (23% vs 22%; $P = .878$).

DISCUSSION

To our knowledge, this is the first study to describe both patient- and asthma-related risk factors for exacerbations during pregnancy among a large cohort of women with asthma. For both outcome definitions, medium-to high-ICS dose and asthma exacerbations in the past 12 months were most strongly associated with exacerbations. In addition, possession of a WAP at the beginning of the study was associated with exacerbations during pregnancy in all models. Overall, this suggests that future exacerbations may be predicted by current and past asthma control and severity, and many of these variables are markers of more severe disease.

In this cohort, 9.2% of women experienced an asthma exacerbation, which is substantially lower than the proportion reported in other studies.[4] Previous studies included GP visits for asthma in their definition of asthma exacerbations, which will have amplified the proportion of recorded asthma exacerbations. For example, in the report of Murphy et al,[12] 26% of women had an unscheduled doctor visit for asthma. Furthermore, for the largest proportion of women included in the current study, for those who participated in the BLT, exacerbations were collected retrospectively instead of prospectively, which may have resulted in fewer recorded exacerbations.

In all models, higher doses of ICS were associated with the highest risk for exacerbations. According to treatment guidelines for asthma during pregnancy, medication doses should be increased when asthma is poorly controlled[41]; this means that higher doses of ICS are likely to be a proxy for more severe and/or uncontrolled asthma. The current data are consistent with

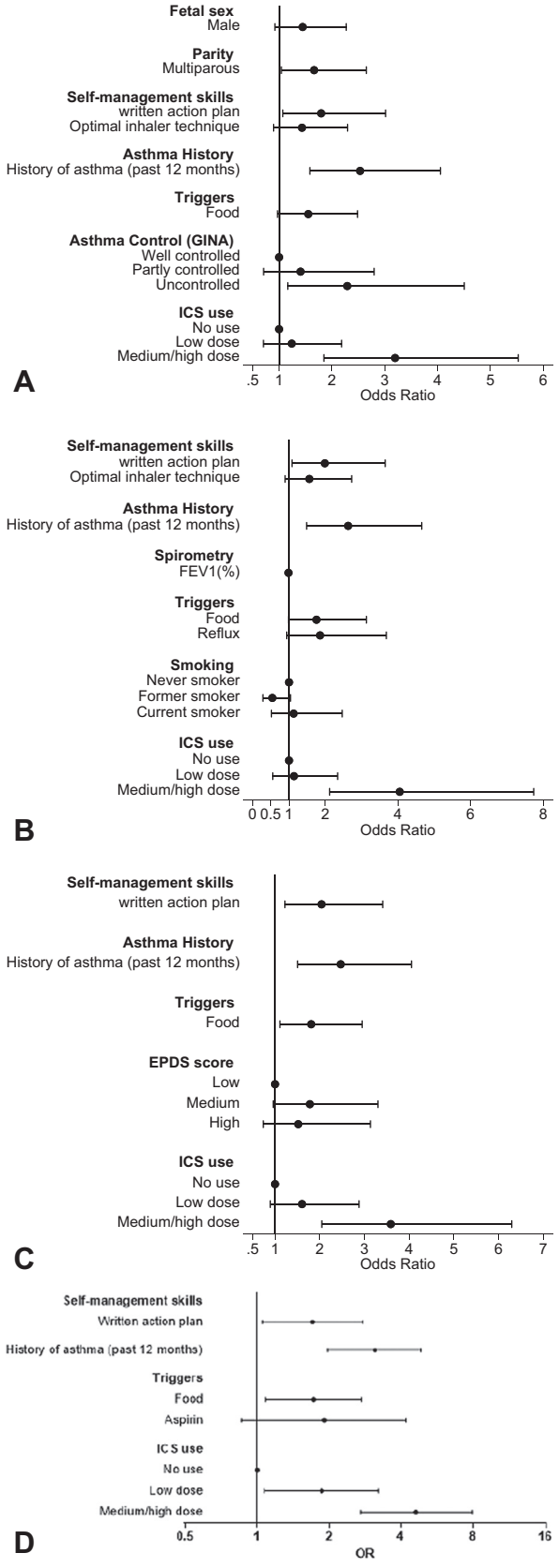

FIGURE 1. Forest plots of logistic regression results. Odds ratios (ORs) are shown with 95% confidence intervals. (**A**) Outcome: severe exacerbation. (**B**) Outcome: oral corticosteroid (OCS) course. (**C**) Outcome: severe exacerbation. Edinburgh Postnatal Depression Scale (EPDS) score and model of care are included. (**D**) Outcome: OCS course. Edinburgh Postnatal Depression Scale score and model of care are included. *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid.

TABLE III. Univariate and multivariate logistic regression of risk factors associated with oral corticosteroid courses for asthma

	Unadjusted			Adjusted (n/N* = 64/1006)		
Variable	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Written action plan	2.722	1.744-4.247	<.001	1.986	1.082-3.648	.027
Good inhaler technique	1.830	1.148-2.918	.011	1.559	0.892-2.724	.119
History asthma exacerbation past 12 mo	4.995	3.275-7.620	<.001	2.628	1.484-4.654	.001
FEV_1 (%)	0.981	0.966-0.996	.014	0.985	0.967-1.003	.108
Trigger: food	2.052	1.342-3.135	.001	1.756	0.985-3.129	.056
Trigger: reflux	2.314	1.421-3.768	.001	1.855	0.936-3.679	.077
Smoking			.144			.135
Never	Reference			Reference		
Former	0.737	0.441-1.230	.243	0.541	0.281-1.040	.065
Current	1.425	0.803-2.527	.226	1.127	0.515-2.464	.765
Inhaled corticosteroid use			<.001			<.001
No use	Reference			Reference		
Low dose (1-500 μg) beclomethasone dipropionate equivalents	2.269	1.340-3.841	.002	1.136	0.552-2.338	.729
Medium/high dose (>500 μg beclomethasone dipropionate equivalents)	6.981	4.238-11.50	<.001	4.048	2.118-7.737	<.001

*Number of exacerbations per total sample size.

previous studies that also identified more severe asthma as a risk factor for future exacerbations[5,12] and no prescribed controller medication as a predictor of low risk for exacerbations.[18] This suggests that despite high-dose ICS (and often ICS or LABA) and optimal management including a written asthma action plan and education, women with more severe asthma have more severe exacerbation in pregnancy. Although it is likely that exacerbation rates would be even higher without appropriate treatment and optimal management, it clearly highlights the need to promote research that trials safe asthma treatments and management approaches in pregnancy that could reduce asthma exacerbations more effectively.

Asthma exacerbations in the past 12 months were significantly associated with exacerbations in all models. Recent exacerbations are the strongest independent predictor of an asthma attack in previous studies of nonpregnant patients, including both adults and children,[42-46] indicating that optimal asthma control is important to reduce the risk for future exacerbations.

The increase in exacerbation risk observed for women who already had a WAP and good inhaler technique before pregnancy may have occurred because these women previously had asthma management optimized owing to more frequent asthma attacks or more severe asthma. Although the *Australian Asthma Handbook*[47] recommends that all people with asthma have an individualized written asthma action plan, only 17.2% of patients in this study who were asked about their WAP actually had one. The *Australian Asthma Handbook* recommends that provision of a WAP and asthma management education be part of postacute care.[47] Therefore, inhaler technique and the presence of a WAP may be proxies for previous exacerbations. A previous study of 169 pregnant women with asthma showed that a nurse-led asthma management service that provided a WAP and asthma management education significantly reduced the risk for loss of control (adjusted relative risk [adjusted risk ratio] = 0.67; 95% CI, 0.46-0.99) and showed a trend toward reduced risk for severe or moderate exacerbations (adjusted risk ratio = 0.69; 95% CI, 0.33-1.42).[48]

Multiparity was associated with severe exacerbations. Most other studies did not observe an association between parity and exacerbation rate.[12,17,26] However, Ali et al[25] also observed an increased risk for exacerbations in multiparous women (adjusted OR = 1.96; 95% CI, 1.28-3.03) and surmised that nulliparous women may have better asthma control because they may prioritize health more than do multiparous women. Murphy et al[12] found that women with severe asthma were significantly more likely to be multiparous than were women with mild asthma ($P < .05$), but did not find a significant increase in exacerbations among multiparous women.

Gastrointestinal reflux as a trigger for asthma was associated with exacerbations and was included in the model for the outcome OCS course. Pregnancy is known to induce gastrointestinal reflux disease or exacerbate preexisting gastrointestinal reflux,[49] which makes it plausible that women whose asthma is triggered by reflux experience more exacerbations during pregnancy, or that reflux becomes a newly recognized trigger for women who had not experienced reflux previously. However, no data were available on reflux treatment.

The AUCs for all models were between 0.7 and 0.8, indicating acceptable or fair discrimination.[50,51] Models were selected using the AIC, which penalizes model fit for model complexity[52] to avoid overfitting.[53] Models resulting from the sensitivity analysis (including EPDS and model of care) contain fewer predictors than do the models from the initial analysis and result in slightly lower AUCs when applied to the entire dataset. This may be because of a lower number of participants included in the model selection: for the outcome severe exacerbations, 39.4% of patients were included in the model selection when EPDS score and model of care were included. Therefore, it would be important to explore the effects of EPDS score and model of care in larger populations.

For the outcome severe exacerbations, EPDS score remained in the final model. We did not include the ACQ score in the analysis because of the high number of missing values (37%) and did not include it in the sensitivity analysis owing to collinearity with asthma control (GINA). Meltzer et al[54] found that the

ACQ score correlated with an increased risk for future exacerbations. It is therefore possible that inclusion of the EPDS score and ACQ would result in a better model if the number of observations were higher. The relationships between EPDS and ACQ score and asthma exacerbations in pregnancy warrant further investigation.

Strengths of this study include the prospective data collection and well-defined study population. Furthermore, the selected models include only variables that are relatively easy and noninvasive to assess in clinical practice, increasing the likelihood that these models could be used in practice.

An important limitation of this study is the difference between the cohorts from which the data were obtained. The studies had slightly differing inclusion and exclusion criteria. Despite this, it is expected that this had only a small impact on the generalizability of the results, because most pregnant women with asthma would have been eligible for these studies. All cohorts excluded women with severe asthma requiring maintenance OCS.

Within the cohorts, participants received different levels of care and different interventions for asthma. In this study, the intervention received by participants was not considered a potential predictor. Because of collinearity between the intervention group (FeNO-guided management vs symptom-based management vs no intervention) and the study (MAP/VEAP vs BLT vs AP II), the intervention group was not included in the model. In the MAP study, FeNO-guided asthma management was associated with a reduced risk for exacerbations.[31] We assumed, however, that the way exacerbations were assessed (prospectively, as in AP II and MAP/VEAP, or retrospectively, as in BLT) may have had a larger impact on the measured rate of exacerbations than the intervention grouping; therefore, we included the study cohort rather than intervention in the model selection.

Although most variables were assessed by the research nurse or midwife, or obtained from medical records, some variables were self-reported. Data concerning asthma history during the past 12 months may be subject to recall bias. Medication adherence was also self-reported, leading to the possibility of both social desirability and recall bias.[39,55] Asthma outcomes were self-reported and confirmed by medical records when possible. We reduced the effects of recall bias and differences in data collection by excluding exacerbations that required only an unscheduled doctor's visit, which might be less likely to be reported by the woman retrospectively and unable to be confirmed objectively.

Preexisting comorbidities and conditions that developed in early pregnancy were not considered possible risk factors in this dataset. Mental health disorders, such as depression and anxiety, have been associated with an increased risk for asthma exacerbations.[22,56] Other studies found that rhinitis[21] and viral infections[12,57] are predictors of exacerbations, associations that were not examined in this study.

This study indicates that current asthma severity and control and exacerbation history are important factors associated with exacerbations during pregnancy. Self-reported asthma triggers were associated with exacerbations. More research is warranted regarding the role of asthma triggers as risk factors for exacerbations during pregnancy, especially the role of food as a trigger. The models selected in this study must be validated before they could be implemented in clinical practice. To increase applicability of the models in clinical practice, it would be useful to develop a prediction rule with a cutoff score for high, medium, and low risk for exacerbations, and asthma management recommendations for each risk category. Because of the potentially severe consequences of exacerbations for both mother and baby, this may help optimize asthma management during pregnancy.

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APPENDIX

Model of Care Coding

Midwifery: HOSPITAL-BASED MIDWIFERY, HOSPITAL BASED MIDWIFERY, BCTMGP, FAMILY CARE MIDWIVES, EARLY STARTERS MIDWIFE, MIDWIFERY TEAM, MIDWIVES CLINIC, FAMILY CARE MIDWIVES, MIDWIFERY-TEAM, MIDWIFERY CASELOAD, BCGP, BIRTH CENTRE TEAM, GPM JUNO, BIRTH CENTRE CARE (MIDWIFES), GPM JUNO

Medical: HOSPITAL-BASED MEDICAL, HOSPITAL BASED MEDICAL, PRIVATE OBSTETRICIAN, GP, DOCTORS CLINIC, HOSPITAL HIGH RISK MATERNITY CARE

Shared care: GP/MIDWIFE SHARED CARE, GP/HOSPITAL MEDICAL SHARED CARE, GP/OBSTETRICIAN SHARED CARE, M3T, SHARED CARE MIDWIFE-OBSTETRICIAN, SHARED ANTENATAL CARE (GP), OBSTETRICIAN/MIDWIFE SHARED CARE, SHARED CARE-HOSPITAL MEDICAL/GP, SHARED CARE GP MIDWIFE, SHARED CARE MIDWIFE/OBSTETRICIAN, SHARED CARE (GP + DOCTORS CLINIC), SHARED CARE MIDWIFE-OBSTETRICIAN, HIGH RISK CLINIC (M3T), SHARED CARE-MIDWIFE/OBSTETRICIAN

Ethnicity coding:

European/Caucasian: ethnicity: CAUCASIAN, CAUCASION, CAUC, WELSH, SCOTTISH, ANGLOSAXON, EURASIAN

Ethnic_identity: AUSTRALIAN_EUROPEAN, BRITISH_EUROPEAN, EUROPEAN, IRISH_EUROPEAN, EASTERN_EUROPEAN, NORTHERN_EUROPEAN, SOUTHERN_EUROPEAN, CENTRAL_WESTERN_EUROPEAN

Aboriginal: ethnicity: ABORIGINAL, ABORIGINAL/TORRES STARIGHT ISLANDER, TORRES STRAIT ISLANDER, AUSTRALIAN/ABORIGINAL

Other/unknown: [all other entries]

TABLE E1. Description of cohorts

Study Characteristic	Management of Asthma in Pregnancy/Viral Exacerbations of Asthma in Pregnancy	Breathing for Life Trial	Phase II Asthma in Pregnancy study
Population	Pregnant women with physician-diagnosed asthma		
Design	Double-blind, parallel, randomized controlled trial	Multicenter parallel, randomized controlled trial	Prospective cohort
N*	311	1200	84
Comparison	Control vs FeNO	Usual care vs FeNO	No intervention
Recruitment	12- to 20-wk gestation	12- to 22 wk gestation	Mean 14.8 wk (SD, 3.0 wk)
Years	June 2007 to December 2010	March 2013 to December 2019	July 2004 to December 2006
Exclusion criteria		Inability to attend monthly study visits. Inability to perform maneuvers required for spirometry or FeNO. Drug or alcohol dependency. Chronic lung disease other than asthma or other chronic illness that may affect participation.	
All patients	Baseline visit plus self-management education Monthly review at antenatal clinic Fortnightly phone calls between visits Usual antenatal appointments	Baseline visit plus self-management education Usual antenatal appointments	Clinic visits at 18, 30, and 36 wk. Fortnightly phone calls between visits. Assessment during exacerbation. Usual antenatal appointments.
Intervention group	Treatment adjusted based on FeNO algorithm through algorithm keeper	Clinic visits every 3-6 wk. Measurement of Asthma Control Questionnaire and FeNO. Treatment adjusted every 2 wk based on FeNO.	-
Control group	Treatment adjusted based on symptoms through algorithm keeper	—	—
Outcome assessment	Prospective during study visits. Postpartum phone call.	Postpartum phone call.	Prospective during study visits. Postpartum phone call.

*Not all patients were included in this study owing to missing outcome data.

TABLE E2. Univariate and multivariate logistic regression of risk factors associated with severe exacerbation: Edinburgh Postnatal Depression Scale and model of care included in model selection

	Unadjusted			Adjusted (n/N* = 89/854)		
Variable	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Written action plan	2.383	1.602-3.546	<.001	2.041	1.221-3.409	.006
History asthma exacerbation past 12 mo	3.872	2.684-5.584	<.001	2.469	1.505-4.052	<.001
Trigger: food	1.967	1.356-2.854	<.001	1.809	1.109-2.949	.017
Edinburgh Postnatal Depression Scale score			.030			.133
Low (≤9)	Reference			Reference		
Medium (10-12)	1.716	0.964-3.053	.066	1.779	0.959-3.302	.068
High (≥13)	2.039	1.085-3.829	.027	1.519	0.737-3.134	.257
Inhaled corticosteroid use			<.001			<.001
No use	Reference			Reference		
Low dose (<500 μg beclomethasone dipropionate)	1.828	1.175-2.845	.007	1.604	0.894-2.879	.113
Medium/high dose (>500 μg beclomethasone dipropionate)	4.815	3.111-7.452	<.001	3.589	2.046-6.295	<.001

*Number of exacerbations per total sample size.

TABLE E3. Univariate and multivariate logistic regression of risk factors associated with severe exacerbation (food as trigger omitted from model selection)

	Unadjusted			Adjusted (n/N* = 95/1174)		
Variable	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Fetal sex: male	1.376	0.956- 1.980	.086	1.474	0.940- 2.312	.091
Parity: multiparous	1.769	1.223- 2.557	.002	1.678	1.054- 2.670	.029
Written action plan	2.383	1.602- 3.546	<.001	1.787	1.067- 2.993	.027
Good inhaler technique	1.656	1.094- 2.507	.017	1.475	0.923- 2.357	.104
History asthma exacerbation past 12 mo	3.872	2.684- 5.584	<.001	2.556	1.601- 4.082	<.001
Global Initiative for Asthma asthma control			<.001			.007
Well-controlled	Reference			Reference		
Partly controlled	1.542	0.880- 2.703	.130	1.484	0.747- 2.948	.260
Uncontrolled	3.489	2.035- 5.980	<.001	2.420	1.231- 4.758	.010
Inhaled corticosteroid use			<.001			<.001
No use	Reference			Reference		
Low dose (1-500 μg beclomethasone dipropionate)	1.828	1.175- 2.845	.007	1.255	0.712- 2.211	.432
Medium/high dose (>500 μg beclomethasone dipropionate)	4.815	3.111- 7.452	<.001	3.270	1.897- 5.635	<.001

*Number of exacerbation per total sample size.

TABLE E4. Univariate and multivariate logistic regression of risk factors associated with oral corticosteroid courses for asthma (food as trigger omitted from model selection)

	Unadjusted			Adjusted (n/N* = 64/1006)		
Variable	Odds ratio	95% confidence interval	*P*	Odds ratio	95% confidence interval	*P*
Written action plan	2.722	1.744- 4.247	<.001	1.925	1.054- 3.515	.033
Good inhaler technique	1.830	1.148- 2.918	.011	1.618	0.929- 2.816	.089
History asthma exacerbation past 12 mo	4.995	3.275- 7.620	<.001	2.691	1.526- 4.746	.001
FEV_1 (%)	0.981	0.966- 0.996	.014	0.984	0.966- 1.002	.080
Trigger: reflux	2.314	1.421- 3.768	.001	1.998	1.022- 3.909	.043
Smoking			.144			.792
Never	Reference					
Former	0.737	0.441- 1.230	.243	0.587	0.308- 1.120	.106
Current	1.425	0.803- 2.527	.226	1.168	0.540- 2.528	.693
Inhaled corticosteroid use			<.001			<.001
No use	Reference					
Low dose (1-500 μg beclomethasone dipropionate equivalents)	2.269	1.340- 3.841	.002	1.178	0.574- 2.418	.655
Medium/high dose (>500 μg beclomethasone dipropionate equivalents)	6.981	4.238- 11.50	<.001	4.133	2.172- 7.866	<.001

*Number of exacerbations per total sample size.

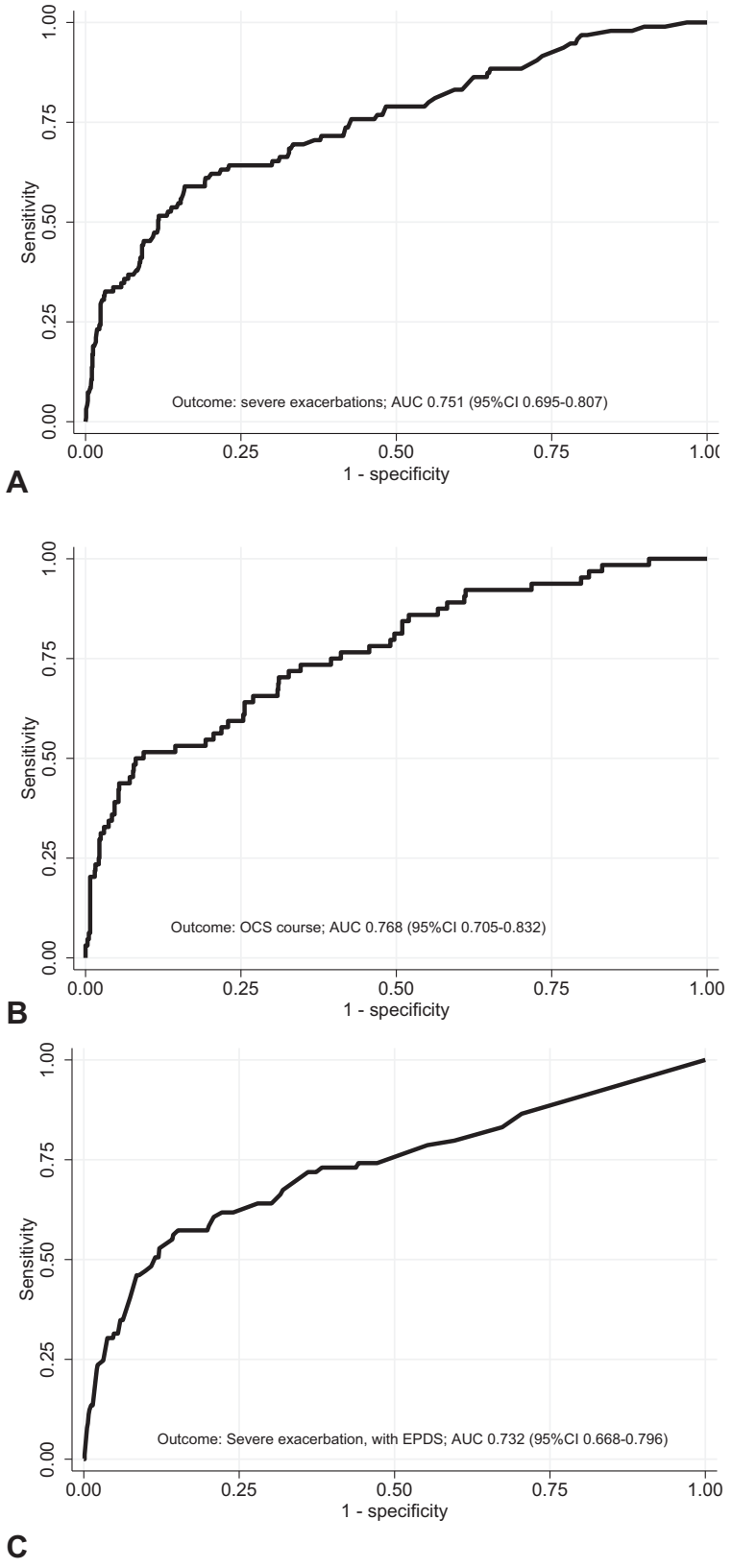

FIGURE E1. Receiver operating characteristic (ROC) curves for selected models with areas under the curve (AUCs). *CI*, confidence interval; *EPDS*, Edinburgh Postnatal Depression Scale; *OCS*, oral corticosteroid.