Original Article

Factors Associated with Nonadherence to Inhaled Corticosteroids for Asthma During Pregnancy

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What is already known about this topic? Nonadherence to inhaled corticosteroids during pregnancy is a clinical problem.

What does this article add to our knowledge? Smoking, higher parity, lower maternal age, adult diagnosis of asthma, and (re-)initiating inhaled corticosteroids during pregnancy are associated with nonadherence to inhaled corticosteroids during pregnancy.

How does this study impact current management guidelines? This study helps identify women who are at increased risk of being nonadherent to inhaled corticosteroids during pregnancy, which may assist health care professionals initiate a more targeted conversation with pregnant women about their asthma medication.

BACKGROUND: Nonadherence is common among pregnant women prescribed inhaled corticosteroids (ICS) for asthma and may have serious consequences for mother and baby. Factors associated with ICS nonadherence have not been determined in this population.

OBJECTIVES: To determine factors associated with {1} nonadherence to ICS in early-mid pregnancy (cross-sectional) and {2} persistent nonadherence to ICS during pregnancy (longitudinal).

METHODS: Data used come from 3 prospective studies (2004-2019) involving women with asthma recruited by 23 weeks' gestation (N = 1614). Demographics, asthma history, and current symptoms were assessed, and spirometry was performed at baseline and throughout pregnancy. Women self-reported current medication use and number of ICS doses missed in the past week. Nonadherence was defined as ≥20% of prescribed dosages missed in the past week (baseline) and on at least 2 occasions during follow-up (persistent). Factors associated with

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Abbreviations used
ACQ- Asthma Control Questionnaire
BMI- Body mass index
CI- Confidence interval
EPDS- Edinburgh Postnatal Depression Scale
F_ENO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
IQR- Interquartile range
LABA- Long-acting β-agonist
OR- Odds ratio
RCT- Randomized controlled trial
ROC- Receiver operating curve

ICS nonadherence were examined using backward stepwise logistic regression.
RESULTS: Of 610 (38%) women prescribed ICS at baseline, 236 (39%) were classified as nonadherent. Of 612 (38%) women prescribed ICS during at least 2 follow-up visits, 149 (24%) were classified as persistent nonadherent. Factors associated with nonadherence at baseline were current or ex-smoking, non-Caucasian/non-Indigenous ethnicity, adult diagnosis of asthma, and lower lung function. Factors associated with persistent nonadherence to ICS were lower maternal age, higher parity, and no prescribed ICS at baseline.
CONCLUSION: Young multiparous non-Caucasian/non-Indigenous mothers are at increased risk of being nonadherent to ICS during pregnancy. Strategies to improve ICS nonadherence should address maternal smoking and target women who (re-)initiate ICS use in pregnancy. **(J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Pregnancy; Asthma; Smoking; Prospective studies; Spirometry*

Asthma affects up to 13% of pregnant women, and is the most common chronic condition during pregnancy.[1] More than one-third of women with asthma have an exacerbation requiring medical intervention during pregnancy.[2,3] Asthma, exacerbations of asthma, and the use of oral corticosteroids during pregnancy are associated with an increased risk of adverse perinatal outcomes, including low birth weight and preterm delivery[4]; however, active management of asthma during pregnancy reduces this risk.[5,6]

Recommended asthma management during pregnancy includes the use of inhaled corticosteroids (ICS) as the predominant controller medication and short-acting β-agonists as reliever medication.[7] However, medication nonadherence during pregnancy is a significant clinical problem,[8] including rates as high as 40% of women with asthma.[9] Studies examining nonadherence to asthma medication in pregnancy are limited,[10-14] and factors associated with ICS nonadherence during pregnancy are largely unknown.

A systematic review reporting on asthma inhaler adherence among nonpregnant adults found that stronger beliefs about treatment necessity were an important factor in controller adherence; yet clinical factors, including smoking, depression, and asthma symptoms, were unrelated to adherence in the majority of studies.[15] It is unknown if this is also true for pregnant women with asthma. The study populations included in the systematic review differed greatly in terms of age, asthma severity, and data source. Furthermore, the definition of nonadherence varied and included self-report adherence, adherence questionnaires, canister weighing, electronic monitoring, and prescription refill records. Therefore, a meta-analysis of these data was not conducted.

ICS nonadherence has been associated with 29% of asthma exacerbations during pregnancy.[16] During pregnancy, uncontrolled asthma may lead to serious perinatal complications.[6] Therefore, adherence to ICS may be particularly important in pregnancy, and there may be factors associated with ICS nonadherence unique to this population that need to be examined.

The aims of this study were to determine factors associated with {1} nonadherence to ICS in early-mid pregnancy in a cross-sectional analysis and {2} persistent nonadherence to ICS during pregnancy in a longitudinal analysis, among women with asthma.

METHODS

Population

Data come from 3 prospective cohorts of pregnant women with asthma recruited between July 2004 and June 2019 via 7 antenatal clinics in Eastern Australia. All cohorts were recruited by 23 weeks' gestation and followed throughout pregnancy until birth.

Cohort 1 was conducted between July 2004 and December 2006 and recruited women with asthma between 17 and 23 weeks' gestation from the John Hunter Hospital (Newcastle, NSW).[3]

Cohort 2 consisted of 2 concurrent studies conducted between April 2007 and November 2009, and recruited women with asthma between 12 and 22 weeks' gestation from the John Hunter Hospital, Newcastle, and the Maitland Hospital, Maitland (NSW).[17,18] One of the 2 studies was a double-blind randomized controlled trial (RCT) of fractional exhaled nitric oxide (F_ENO)-based management versus symptom-based management, the Managing Asthma in Pregnancy study.

Cohort 3 was an RCT of asthma treatment adjustment with F_ENO-based management versus usual care between March 2013 and June 2019, the Breathing for Life Trial.[19] Women with asthma were recruited between 12 and 23 weeks' gestation from the John Hunter Hospital, Newcastle (NSW); Royal North Shore Hospital, Royal Hospital for Women Randwick and Nepean Hospital, Sydney (NSW); Royal Brisbane and Women's Hospital, Brisbane (QLD); and The Canberra Hospital, Canberra (ACT). Ethical approval was obtained for all studies from the Hunter New England Health Human Research Ethics Committee and the University of Newcastle (Reference numbers: Cohort 1: 9709173.07, Cohort 2: 07/02/21/3.06, and Cohort 3: 12/10/17/3.04). Written informed consent was obtained from all women before participation.

Measurements

Baseline data from all 3 cohorts included maternal age, body mass index (BMI, kg/m^2), gestational age at recruitment, self-reported smoking status (never, ex, or current), ethnicity (Caucasian, Indigenous, or non-Caucasian/non-Indigenous), employment, asthma history (age at diagnosis [continuous, and grouped as <18 and ≥ 18 years], and health care utilization in past 2 years), asthma triggers (season, reflux, exercise, upper respiratory tract infection, work, pets, food, aspirin, and fumes), and current asthma symptoms and medication use. Socioeconomic status was determined based on

postcode and Socio-Economic Index For Areas (SEIFA 2016).[20] In cohorts 1 and 3, participants were asked to think about the time their asthma symptoms were at their best and to report their ICS dose at that time ("ICS dose at best"); this was categorized as "No ICS at best" (ICS dose at best reported as zero) and "ICS at best" (ICS dose >0 μg/day at best reported). Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured by spirometry (cohort 1: Spirotac IV, Vitalograph, Buckingham, UK; cohorts 2 and 3: EasyOne Spirometer, NicheMedical, North Sydney, Australia), and age- and height-adjusted percent predicted FEV_1 and FVC (%) values were calculated using the NHANESIII.[21] Airway inflammation was assessed by measuring F_ENO among all participants in cohorts 1 (NIOX, Aerocrine, Solna, Sweden) and 2 (ECOMEDICS, Dürnten, Switzerland), and only in those randomized to the intervention group in cohort 3 (NIOX MINO, Aerocrine, Solna, Sweden). The F_ENO levels measured by NIOX/NIOX MINO were converted to ECOMEDICS levels for comparison using in-house validated equations.[11] Asthma control was assessed using the validated Asthma Control Questionnaire (ACQ)[22] in all women, except those randomized to the control group in cohort 3, with uncontrolled asthma defined as ACQ score ≥1.5.[23] In addition, asthma control was categorized as "well-controlled," "partly controlled," or "uncontrolled," based on the Global Initiative for Asthma (GINA) guidelines, using reliever use in the past week, night, and morning symptoms, and activity limitation.[24]

Asthma self-management skills were assessed as previously described[11] and included medication knowledge and inhaler technique. Participants in each clinical trial received asthma self-management education regarding self-management skills, asthma control, and adherence at each study visit.[11] ICS use and adherence were self-reported by asking how many ICS dosages were missed in the past week.[11,14] The Edinburgh Postnatal Depression Scale[25] (EPDS) was recorded from the woman's first antenatal appointment for those in Newcastle and Maitland; score ranges from 0 to 30 (score ≥10 warrants psychological review and/or assessment[26]).

Statistical analysis

All data were analyzed using Stata IC version 15 (StataCorp, College Station, TX). At baseline, women were classified as nonadherent if they had missed ≥20% of their prescribed ICS doses in the past week.[11] For the persistent nonadherence analysis, we included women who had at least 2 follow-up visits during pregnancy where ICS adherence data were collected. Persistent nonadherence during pregnancy was defined as being nonadherent (based on the aforementioned definition) at 2 or more follow-up visits, where ICS was prescribed, during pregnancy (ie, excluding the baseline visit).

Data were presented as mean ± standard deviation, median [interquartile range, IQR], or n/N (%) unless otherwise stated. Continuous variables were compared between adherent and nonadherent women using 1-way analysis of variance or the Kruskal-Wallis test as appropriate. Dichotomous variables were analyzed using χ^2 tests. The statistical significance threshold was set at the 0.05 level. Factors that may be associated with baseline nonadherence and persistent nonadherence ($P \leq .2$) were explored with backward stepwise logistic regression models and expressed as odds ratios (ORs) for the crude analyses and adjusted ORs for the final model. We used the Akaike Information Criteria and the Bayesian Information Criteria to identify the best fitting models. Goodness of fit of the final models was assessed using the Hosmer-Lemeshow χ^2 test with 10 subgroups, where $P > .05$ indicated a satisfactory model. The area under the receiver operating curve (ROC) was determined for the best fitting model. Because of anticipated missing data for potentially important factors associated with nonadherence, we performed sensitivity analyses restricting the dataset to those where these data were collected. For the baseline analysis, a sensitivity analysis was done with "ICS at best." For the longitudinal analysis, sensitivity analyses were performed with "ICS at best" and EPDS.

RESULTS

Baseline nonadherence

In total, 1614 women were included from the 3 cohorts, of whom 610 (38%) were prescribed ICS at baseline (approximately 19 weeks' gestation). Among these women, 236 (39%) were nonadherent to their prescribed treatment (Figure 1). The majority of women in the non-Caucasian/non-Indigenous group were Asian, Maori/Pacific Islander, and Hispanic. Women in the nonadherent group were more likely to use ICS/long-acting β-agonist (LABA) combination therapy ($P = .01$), more likely to have been diagnosed with asthma as an adult ($P < .01$), and more likely to smoke ($P = .01$), compared with women in the adherent group. Nonadherent women had a lower FEV_1% predicted ($P = .02$) and higher F_ENO levels ($P = .01$) compared with adherent women. Asthma control status did not differ between adherent and nonadherent women, whether based on GINA guidelines ($P = .27$) or ACQ ($P = .46$) (Table I).

The multivariable model included smoking status, ethnicity, adult diagnosis, several asthma triggers (food, aspirin, and seasonal changes), ICS/LABA combination therapy use, history of emergency department visits for asthma, and FEV_1% predicted (Table II). For the adjusted model, the area under the ROC was 67% (95% confidence interval [CI]: 62%-72%); the goodness of fit test had a P value of .24. Current smokers and non-Caucasian/non-Indigenous women were 2.1 times more likely to be nonadherent compared with never smokers and Caucasian women, respectively. Ex-smokers were 71% more likely to be nonadherent than never smokers. Women diagnosed with asthma as an adult were almost twice as likely to be nonadherent compared with women diagnosed in childhood. A higher FEV_1% predicted reduced the odds of being nonadherent by 10% for each 5% increase of FEV_1% predicted (Figure 2).

In the sensitivity analysis, restricting to those with data on "ICS at best" (n = 490, 80%), women who reported using ICS "at best" were 70% less likely to be nonadherent. The final model additionally included ethnic identity, adult diagnosis, work and food as an asthma trigger, and FEV_1% predicted (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The area under the ROC was 71% (95% CI: 65%-76%); the goodness of fit test had a P value of .67.

Persistent nonadherence

Of 1614 women, 876 (54%) had at least 2 follow-up visits during pregnancy. Of these women, 612 (70%) had nonadherence data from 2 or more follow-up visits and were included in the longitudinal analysis; 149 (24%) were classified as persistently nonadherent (Figure 1). The median number of visits in both adherence groups was 4 [IQR: 3, 5].

Persistent nonadherence to ICS was associated with smoking at baseline ($P = .03$) and unemployment ($P = .02$). Persistently nonadherent women were more likely to have uncontrolled asthma at baseline compared with adherent women (GINA $P = .02$ or ACQ $P < .01$) (Table III). Women prescribed ICS medication at

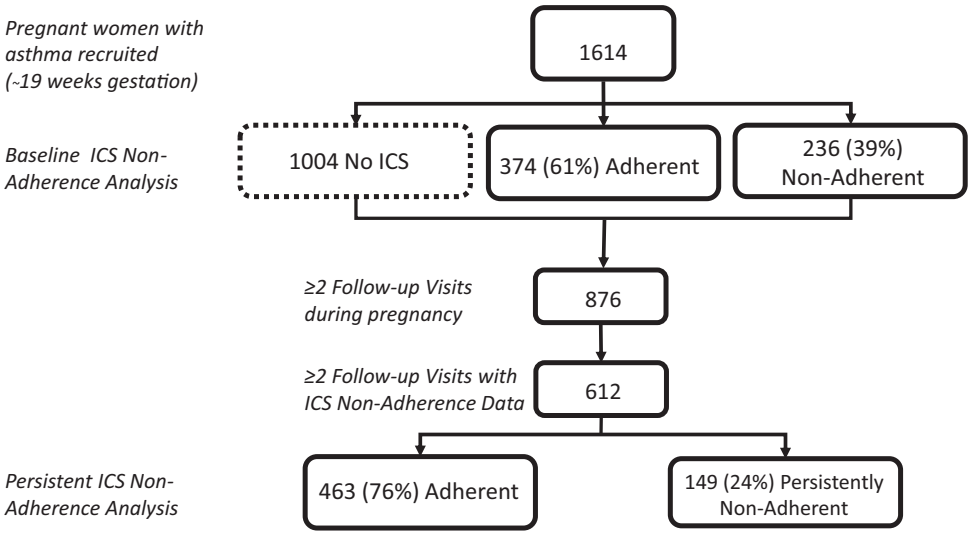

FIGURE 1. Study population flow diagram. *ICS,* Inhaled corticosteroid.

baseline were less likely to be nonadherent during pregnancy compared with women who were not prescribed ICS at baseline ($P < .01$). Furthermore, women who were nonadherent to prescribed ICS treatment at baseline were more likely to remain nonadherent throughout pregnancy compared with women who were adherent at baseline ($P < .01$) (Figure 3).

The multivariate model for the persistent nonadherence analysis included maternal age, ICS treatment at baseline, and parity (Table IV). The area under the ROC was 67% (95% CI: 63%-72%); the goodness of fit test had a *P* value of .66. Compared with non-ICS users at baseline, women who were ICS adherent at baseline were 72% less likely to be persistently nonadherent. Furthermore, increased parity increased the odds of persistent nonadherence by 24% per viable pregnancy. In contrast, increasing maternal age was associated with a 5% reduced odds of persistent nonadherence per year.

In the first sensitivity analysis, restricting to those with data on ICS "at best" (n = 405, 66%), the multivariate model with the best fit included ICS "at best," baseline smoking status, ICS treatment, BMI, and employment status. Women who reported using ICS "at best" were 46% less likely to be persistently nonadherent during pregnancy than women who reported not to use ICS "at best." The area under the ROC was 74% (95% CI: 68%-79%), and the goodness of fit had a *P* value of .70 (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

In the second sensitivity analysis for persistent nonadherence, restricting to those with EPDS data available (n = 445, 73%), the final model included maternal age, ICS treatment at baseline, parity, and the total EPDS score. The model and estimates were similar to the main analysis for persistent nonadherence with the inclusion of the EPDS score. With each point increase in EPDS score, women were 6% more likely to be persistently nonadherent. The area under the ROC was 68% (95% CI: 63%-74%) and the goodness of fit had a *P* value of .70 (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This is the first study to report clinical characteristics associated with ICS nonadherence in women with asthma during pregnancy, of whom 39% were nonadherent to their prescribed ICS treatment at baseline (approximately 19 weeks' gestation), and 24% were persistently nonadherent throughout pregnancy, despite follow-up visits that included asthma education.[11] Factors associated with nonadherence at baseline were non-Caucasian/non-Indigenous ethnicity, current or ex-smoking status, being diagnosed with asthma as an adult, and a lower FEV_1%. Factors associated with persistent nonadherence to ICS throughout pregnancy were younger maternal age, increased parity, and no prescribed ICS at baseline. As most of these variables are routinely collected in antenatal care, clinicians could use these data to identify women who are at increased risk of nonadherence during pregnancy and undertake targeted strategies aimed at improving ICS adherence in pregnancy. However, additional ways to identify target high-risk women are needed.

We used a commonly used value of 20% missed doses to determine ICS nonadherence. In the systematic review of Dima et al,[15] 12 studies (where all but one used objective measures) reported cutoff values for nonadherence (ranging from 15% to 50%) with half of them using the 20% cutoff. Previous research in children with asthma linked this level of nonadherence with worse asthma control.[27] Interestingly, we did not observe a difference in asthma control status between the adherent and nonadherent groups, as might be expected. This might be due to the simultaneous measurement of nonadherence and asthma control. Williams et al[28] reported that adults with ICS nonadherence of <25% experienced the primary treatment benefit, for example, prevention of exacerbations. The 20% cutoff may be a good balance between realistic patient behavior (missing 20% of weekly dosages approximates missing 1 daily dose of asthma medication per week) and clinical efficacy; however, pharmacoepidemiological evidence for this cutoff value is still needed.

The current literature does not have a definition for persistent nonadherence. Grzeskowiak et al[29] defined persistent uncontrolled asthma during pregnancy as having an ACQ6 $\geq$ 1.5 at 2 or more visits during pregnancy (8 weeks apart). We defined persistent nonadherence as being nonadherent at 2 or more visits 4 to 6 weeks apart, which corresponds closely with recommendation for monthly asthma assessment during pregnancy.[24]

TABLE I. Baseline characteristics of women with asthma, classified as adherent vs nonadherent to inhaled corticosteroids, at baseline

	Adherent (n = 374)	Nonadherent (n = 236)	*P* value
Clinical trial, n (%)			.48
Cohort 1	22 (6)	14 (6)	
Cohort 2	53 (14)	42 (18)	
Cohort 3	299 (80)	180 (76)	
Maternal demographics			
Age (y)	30.6 ± 5.3	30.8 ± 5.6	.62
Gestational age at recruitment (weeks)	18.6 [16.3, 20.9]	18.8 [16.3, 20.6]	.81
BMI (kg/m^2)	27.1 [24.0, 32.8] n = 370	26.8 [23.6, 33.1] n = 235	.32
BMI categories, n/N (%)			.36
Nonoverweight [<25 kg/m^2]	112/370 (30)	84/235 (36)	
Overweight [25-29.9 kg/m^2]	120/370 (32)	72/235 (31)	
Obese [≥30 kg/m^2]	138/370 (37)	79/235 (34)	
Smoking status, n/N (%)			**<.01**
Never	218/352 (62)	113/226 (50)	
Ex	107/352 (30)	76/226 (34)	
Current	27/352 (8)	37/226 (16)	
Employed, n/N (%)	253/336 (75)	162/213 (76)	.84
Ethnicity, n/N (%)			**.03**
Caucasian	305/347 (88)	173/217 (80)	
Indigenous	14/347 (4)	14/217 (6)	
Non-Caucasian/non-Indigenous*	28/347 (8)	30/217 (14)	
Socioeconomic Indexes for Areas quintiles, n (%)			.97
First quintile (lowest SES)	42 (11)	24 (10)	
Second quintile	38 (10)	25 (11)	
Third quintile	129 (34)	84 (36)	
Fourth quintile	97 (26)	64 (27)	
Fifth quintile (highest SES)	68 (18)	39 (17)	
Gravida (n)	2 [1, 3] n = 365	2 [1, 3] n = 230	.49
Parity (n)	0 [0, 1] n = 365	1 [0, 2] n = 230	.13
Multiparous, n/N (%)	181/365 (50)	126/230 (55)	.22
Prenatal EPDS score	5 [2, 9] n = 211	5 [2, 9] n = 135	.93
Asthma-related			
Asthma history			
Age at diagnosis (y)	4.5 [2.0, 9.0] n = 361	6.0 [2.0, 13.0] n = 228	**.03**
Adult diagnosis (≥18 y), n/N (%)	36/361 (10)	41/228 (18)	**<.01**
≥1 hospitalization in past 2 y, n/N (%)	26/371 (7)	14/235 (6)	.63
≥1 ED visit in past 2 y, n/N (%)	59/371 (16)	27/235 (12)	.14
≥1 OCS course in past 2 y, n/N (%)	104/371 (28)	59/234 (25)	.45
ICS use "at best," n/N (%)	233/307 (76)	94/183 (51)	**<.01**
Triggers, n/N (%)			
Season	325/373 (87)	214/235 (91)	.14
Reflux	53/374 (14)	33/235 (14)	.96
Exercise	289/374 (77)	184/235 (78)	.77
URTI	333/373 (89)	207/235 (88)	.65
Work	50/374 (13)	46/235 (20)	**.04**
Pets	181/374 (48)	103/235 (44)	.27
Food	119/374 (32)	57/235 (24)	**.05**
Aspirin	24/374 (6)	8/235 (3)	.10
Fumes	252/374 (67)	157/235 (67)	.88
Current asthma symptoms			
ACQ score	1.29 [0.71, 2.14] n = 237	1.43 [0.71, 2.18] n = 142	.61
Uncontrolled asthma (ACQ ≥ 1.5), n/N (%)	106/237 (45)	69/142 (49)	.46
GINA control status			.27
Well controlled	72/370 (20)	34/233 (15)	

(continued)

TABLE I. *(Continued)*

	Adherent (n = 374)	Nonadherent (n = 236)	*P* value
Partly controlled	147/370 (40)	103/233 (44)	
Uncontrolled	151/370 (41)	96/233 (41)	
Lung function			
FEV_1 % predicted	91.8 [81.4, 99.9] n = 323	87.7 [77.6, 98.2] n = 211	**.02**
FVC % predicted	94.5 [86.5, 103.2] n = 321	92.7 [83.2, 102.6] n = 208	.18
FEV_1:FVC ratio (%)	81.3 [76.1, 85.1] n = 321	79.6 [73.8, 84.8] n = 208	**.03**
F_ENO (ppb)	14.4 [9.2, 25.0] n = 224	19.6 [11.0, 33.0] n = 132	**.01**
Asthma medications			
ICS/LABA combination, n (%)	272 (73)	192 (81)	**.01**
BDP equivalent ICS dose (μg/d)	400 [250, 800] n = 369	400 [250, 800] n = 229	.84
Reliever use in the past week (times)	4 [1, 12] n = 367	4 [0, 8] n = 232	**.43**
Asthma self-management skills, n/N (%)			
Correct reliever knowledge	128/338 (38)	73/213 (34)	.39
Correct controller knowledge	97/338 (29)	47/212 (22)	.09
Optimal pMDI technique	108/312 (35)	69/202 (34)	.92
Optimal turbuhaler technique	103/297 (35)	66/180 (37)	.66
WAP possession	93/369 (25)	56/233 (24)	.71

ACQ, Asthma Control Questionnaire; *BDP*, beclomethasone dipropionate; *BMI*, body mass index; *ED*, emergency department; *EPDS*, Edinburgh Postnatal Depression Score; *F_ENO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *OCS*, oral corticosteroid; *pMDI*, pressurized Metered Dose Inhaler; *SES*, socioeconomic status; *URTI*, upper respiratory tract infection; *WAP*, Written Action Plan.

Data presented as n/N (%) for categorical variables with missing data, n (%) for categorical variables without missing data, median [interquartile range or mean ± standard deviation]. Percentages may add up over or not up to 100% due to rounding.

Bold values indicate significant results.

*Non-Caucasian/non-Indigenous ethnicity includes African, Asian, South American, Middle Eastern, Pacific Islander, and Maori.

TABLE II. Crude and adjusted odds of nonadherence to inhaled corticosteroids at baseline in pregnancy among women with asthma

Variable	Crude OR 95% CI	*P* value	Adjusted* OR 95% CI	*P* value
Smoking status				
Never	Reference		Reference	
Ex	1.37 (0.95-1.99)	.097	**1.71 (1.09-2.67)**	**.019**
Current	**2.64 (1.53-4.56)**	**<.001**	**2.13 (1.10-4.11)**	**.025**
Ethnic identity				
Caucasian	Reference		Reference	
Indigenous	1.76 (0.82-3.78)	.146	1.67 (0.67-4.16)	.268
Non-Caucasian/non-Indigenous	**1.89 (1.09-3.27)**	**.023**	**2.16 (1.08-4.29)**	**.029**
ED visit in past 2 y	0.69 (0.42-1.13)	.139	0.57 (0.30-1.09)	.091
Adult diagnosis	**1.98 (1.22-3.21)**	**.006**	**1.97 (1.10-3.53)**	**.022**
Trigger—work	**1.58 (1.02-2.45)**	**.042**	1.59 (0.92-2.75)	.095
Trigger—food	**0.69 (0.47-0.99)**	**.046**	0.65 (0.41-1.03)	.069
Trigger—aspirin	0.51 (0.23-1.16)	.110	0.37 (0.12-1.16)	.090
FEV_1 % predicted (per %)	**0.99 (0.97-1.00)**	**.022**	**0.98 (0.97-1.00)**	**.029**
ICS/LABA combination use	**1.64 (1.10-2.44)**	**.016**	1.59 (0.97-2.61)	.068

CI, Confidence interval; *ED*, emergency department; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *OR*, odds ratio.

Bold values indicate significant results.

*Adjusted for all other variables in model.

Because our study employed visit intervals that are common in obstetric care, we are confident that our results represent those of normal clinical practice. Furthermore, these visits provide opportunities for health care providers to identify women who are nonadherent and institute interventions, including providing education on the importance of medication use.

Our results show a significantly increased risk of nonadherence for women who report a smoking history at baseline. This is in contrast to a previous systematic review examining asthma inhaler adherence among adults,[15] which found that self-reported smoking status (varying definitions including pack years, ever vs not, current/ex/never) was not associated with adherence. However, the studies in the review had small numbers of participants prescribed ICS medications and all studies used a different measure of adherence (varying from questionnaires to prescription refill), whereas our study population was larger and included 610 women using ICS. Future research regarding ICS adherence during pregnancy should examine reasons women continue smoking and evaluate whether these reasons also affect other health behaviors such as

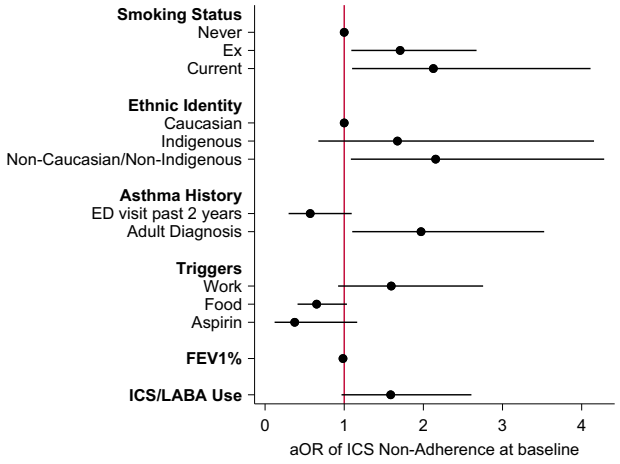

FIGURE 2. Adjusted odds ratios (aORs) for inhaled corticosteroid (ICS) nonadherence at baseline. *ED*, Emergency department; *FEV_1*, forced expiratory volume in 1 second, *LABA*, long-acting β-agonist.

medication adherence. Our results also show that women with a non-Caucasian/non-Indigenous ethnicity were more likely to be nonadherent compared with women with a Caucasian ethnicity. The immigrant population in Australia is large and growing, with 29% of the population born overseas in 2017.[30] Reasons for nonadherence in this population may be found in language barriers or cultural differences, differences in prescribing practices, access to care, or response to therapy as a result of differing phenotypes. It is likely that medication use and adherence is related to multiple factors that we have not measured in our study, such as other social determinants of health, including poverty, adverse childhood experiences, family unemployment, and substance use. Understanding these aspects may inform the development of appropriate interventions, which are personalized as well as culturally and linguistically diverse, to improve asthma medication adherence in pregnancy.

Our results show that women who were ICS adherent at baseline were more likely to be adherent throughout pregnancy compared with women who did not use ICS at baseline. This is consistent with previous research, which has shown that past medication behavior may be a good predictor of future medication behaviour.[31] It is unknown whether the women who did not use ICS at baseline were steroid-naïve or whether they had stopped their ICS treatment in early pregnancy (commonly observed in other studies[32,33]), even though it was indicated for them before enrollment. This decision is often made by the woman herself without consulting a physician.[34,35] These women may have specific medication beliefs that influence ICS adherence during pregnancy,[36,37] especially when ICS is (re-) initiated. Future work may benefit from collecting this information as it may help refine information packages about asthma medication, specifically for those of childbearing age and pregnant women. This information may also benefit health care providers by helping facilitate discussion with pregnant women (and those planning a pregnancy) about concerns they may have about their asthma medication. Our study found that young women, and women with children, were more likely to be nonadherent during pregnancy. Younger women may have more social barriers[38] than older women, which may contribute to medication nonadherence. In contrast to the reduced risk for older women, women who already have a child were also at increased risk of persistent nonadherence. The reasons for this are unknown.

In our sensitivity analyses we found 2 additional factors that warrant further investigation in a larger population, ICS "at best" and the EPDS. In both cross-sectional and longitudinal sensitivity analyses, ICS "at best" seems to have an association with adherence. Previous research has indicated that a higher level of perceived need for medication is associated with lower nonadherence.[15,39] Although we did not measure perceived need in our study population, reporting no ICS "at best" may be related to a lower perceived need for the medication[40] or an underestimation of asthma severity or symptom control; however, this has not been previously explored. A limitation of this question was that we did not ask women to identify their best asthma control during a specific time period, either during pregnancy, or before pregnancy. Given that asthma is a dynamic disease, asthma control and need for ICS medication may change over time.

In addition, women with higher EPDS scores were at increased odds of persistent nonadherence. Mental health problems have previously been found to be associated with ICS nonadherence among adults with severe poorly controlled asthma,[41] and are common during pregnancy,[42] especially among women with asthma.[43] Furthermore, women with depressive symptoms are more likely to have uncontrolled asthma during pregnancy compared with women without depressive symptoms.[44] Our results demonstrate the importance of mental health assessment among pregnant women with asthma, especially in those who might be more likely to be nonadherent.

This study has several strengths. First, we were able to include a relatively large population of pregnant women with asthma. The women were recruited through antenatal clinics, where the majority of pregnant women in Australia receive their care; therefore, our study population is a good representation of the Metropolitan and regional population of Australia. Although the data came from 3 different cohorts, the education provided on asthma and medication use was consistent across cohorts, and has previously been shown to have similar effects on adherence.[11] Therefore, these 3 cohorts were combined to identify clinical factors related to nonadherence. All cohorts used validated questionnaires to assess asthma control (ACQ) and perinatal depression (EDPS), with asthma control additionally determined based on the definition used in the GINA guidelines.[24]

This study also has some limitations, in particular the use of self-reported nonadherence. This could have led to social desirability bias, resulting in the level of nonadherence in our study being an underestimation. However, a previous study suggests, based on the comparison between self-reported adherence and medication possession rates before and during pregnancy among women with asthma, that self-reported medication adherence may be more accurate during pregnancy compared with outside of pregnancy.[12] Furthermore, we may have underestimated ICS nonadherence due to selection bias. Women who do not participate in research studies might not see asthma as an important issue during pregnancy and therefore may be more likely to be nonadherent. Also, we may have underestimated complete nonadherence (eg, women who stopped using ICS in early pregnancy, even when needed). We did not assign asthma

TABLE III. Baseline characteristics of women with asthma, classified as adherent vs persistently nonadherent to inhaled corticosteroids during pregnancy

	Adherent (n = 463)	Persistent nonadherent (n = 149)	*P* value
Clinical trial, n (%)			.09
Cohort 1	30 (7)	4 (3)	
Cohort 2	125 (27)	50 (34)	
Cohort 3	308 (67)	95 (64)	
Maternal demographics			
Age (y)	29.9 (5.4)	28.8 (5.6)	**.02**
Gestational age at recruitment (weeks)	18.0 [15.6, 20.4]	18.1 [15.6, 19.9]	.32
BMI (kg/m^2)	27.5 [23.9, 33.4]	29.0 [24.2, 32.9]	.20
BMI categories, n (%)			.34
Nonoverweight [<25 kg/m^2]	149 (32)	42 (28)	
Overweight [25-29.9 kg/m^2]	146 (32)	43 (29)	
Obese [≥30 kg/m^2]	168 (36)	64 (43)	
Smoking status, n/N (%)			**.02**
Never	263/445 (59)	69/142 (49)	
Ex	132/445 (30)	45/142 (32)	
Current	50/445 (11)	28/142 (20)	
Employed, n/N (%)	299/407 (74)	78/125 (62)	**.02**
Ethnicity, n/N (%)			.84
Caucasian	378/436 (87)	115/135 (85)	
Indigenous	26/436 (6)	8/135 (6)	
Non-Caucasian/non-Indigenous*	32/436 (7)	12/135 (9)	
Socioeconomic Indexes for Areas quintiles, n (%)			.10
First quintile (lowest SES)	50 (11)	19 (13)	
Second quintile	55 (12)	16 (11)	
Third quintile	185 (40)	70 (47)	
Fourth quintile	108 (23)	35 (23)	
Fifth quintile (highest SES)	65 (14)	9 (6)	
Gravida (n)	2 [1, 3] n = 460	2 [2, 4]	**.02**
Parity (n)	1 [0, 1] n = 460	1 [0, 2]	.07
Multiparous, n/N (%)	238/460 (52)	89 (60)	.09
Prenatal EPDS score	5.0 [2.0, 8.8] n = 296	6.0 [4.0, 10.0]	**.02**
Asthma-related			
Asthma history			
Age at diagnosis (y)	5.0 [2.0, 12.0] n = 448	5.0 [3.0, 13.0] n = 144	.62
Adult diagnosis (≥18 y)	59/448 (13)	22/144 (15)	.52
≥1 hospitalization in past 2 y, n/N (%)	25/460 (5)	6 (4)	.50
≥1 ED visit in past 2 y, n/N (%)	60/460 (13)	19 (13)	.93
≥1 OCS course in past 2 y, n/N (%)	104/460 (23)	27 (18)	.25
ICS use "at best," n (%)	165/315 (52)	28/90 (31)	**<.01**
Triggers, n/N (%)			
Season	414/462 (90)	132 (89)	.73
Reflux	62/462 (13)	18/148 (12)	.74
Exercise	376 (81)	123 (83)	.71
URTI	414 (89)	132 (89)	.78
Work	87 (19)	24 (16)	.49
Pets	202 (44)	64 (43)	.87
Food	120 (26)	46 (31)	.22
Aspirin	22 (5)	8/148 (5)	.75
Fumes	339 (73)	105 (71)	.52
Current asthma symptoms			
ACQ score	1.31 [0.71, 2.14] n = 462	1.71 [1.00, 2.29]	**<.01**
Uncontrolled asthma (ACQ ≥ 1.5), n/N (%)	210/462 (46)	90 (60)	**<.01**
GINA control status, n/N (%)			**.02**
Well controlled	89/459 (19)	16/147 (11)	

(continued)

TABLE III. *(Continued)*

	Adherent (n = 463)	Persistent nonadherent (n = 149)	*P* value
Partly controlled	194/459 (42)	58/147 (40)	
Uncontrolled	176/459 (38)	73/147 (50)	
Lung function			
FEV_1 % predicted	89.6 [80.6, 98.5] n = 401	88.4 [79.9, 98.4] n = 129	.58
FVC % predicted	93.9 [84.8, 103.1] n = 400	94.47 [86.9, 102.3] n = 127	.95
FEV_1:FVC %	81.2 [75.4, 85.0] n = 399	80.7 [74.0, 86.0] n = 127	.83
F_ENO (ppb)	19.0 [11.0, 36.9] n = 445	17.0 [8.0, 35.0] n = 144	.05
Medication use at baseline			
ICS	276 (60)	58 (39)	**<.01**
ICS/LABA combination, n/N (%)	213/276 (77)	42/58 (72)	.43
ICS dose (BDP equivalent, µg/d)	400 [250, 800] n = 269	800 [363, 800] n = 58	**.02**
ICS treatment at baseline, n/N (%)			**<.01**
Nonuser	187/455 (41)	91/148 (62)	
Adherent	186/455 (41)	23/148 (16)	
Nonadherent	82/455 (18)	34/148 (23)	
Reliever use in the past week (times)	4 [0, 8] n = 456	4 [0, 7] n = 146	**.72**
Self-management skills, n/N (%)			
Correct reliever knowledge	125/416 (30)	28/132 (21)	.05
Correct controller knowledge	66/319 (21)	15/91 (17)	.39
Optimal pMDI technique	124/410 (30)	34/133 (26)	.32
Optimal turbuhaler technique	107/330 (32)	27/102 (27)	.26
WAP possession	105/458 (23)	25/147 (17)	.13

ACQ, Asthma Control Questionnaire; *BDP*, beclomethasone dipropionate; *BMI*, body mass index; *ED*, emergency department; *EPDS*, Edinburgh Postnatal Depression Score; *F_ENO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *OCS*, oral corticosteroid; *pMDI*, pressurized Metered Dose Inhaler; *SES*, socioeconomic status; *URTI*, upper respiratory tract infection; *WAP*, Written Action Plan.

Data presented as n/N (%) for categorical variables with missing data, n (%) for categorical variables without missing data, median [interquartile range or mean ± standard deviation]. Percentages may add up over or not up to 100% due to rounding.

Bold values indicate significant results.

*Non-Caucasian/non-Indigenous ethnicity includes African, Asian, South American, Middle Eastern, Pacific Islander, and Maori.

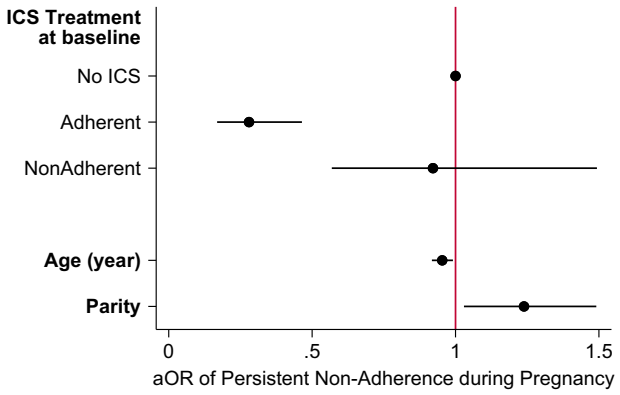

FIGURE 3. Adjusted odds ratios (aORs) for persistent inhaled corticosteroid (ICS) nonadherence during pregnancy.

TABLE IV. Crude and adjusted odds of persistent nonadherence to inhaled corticosteroids during pregnancy among women with asthma

Variable	Crude OR 95% CI	*P* value	Adjusted* OR 95% CI	*P* value
ICS treatment at baseline				
No use	Reference		Reference	
Adherent	**0.25 (0.15-0.42)**	**<.001**	**0.28 (0.17-0.46)**	**<.001**
Nonadherent	0.85 (0.53-1.37)	.506	0.92 (0.57-1.49)	.740
Age (y)	**0.96 (0.93-1.00)**	**.025**	**0.95 (0.92-0.99)**	**.015**
Parity (n)	**1.18 (1.00-1.39)**	**.048**	**1.24 (1.03-1.49)**	**.023**

CI, Confidence interval; *ICS*, inhaled corticosteroid; *OR*, odds ratio.

Bold values indicate significant results.

*Adjusted for all other variables in model.

phenotypes to the women in this study, and women with T2-low asthma may have a different response to ICS medications,[45] which could impact adherence. Other factors that may be associated with nonadherence, such as pre-existing and pregnancy-related comorbidities and polypharmacy, could be explored in future studies.

More research is needed to determine the reasons for ICS nonadherence during pregnancy among women with asthma, focusing on the specific risk factors identified in this study. In addition, future research needs to determine the impact of ICS nonadherence during pregnancy on asthma- and pregnancy-related health outcomes for the mother and infant. For health care providers managing women with asthma during pregnancy, it is important to identify risk factors for ICS nonadherence and develop strategies for improving adherence in these groups.

In conclusion, to improve ICS adherence among women with asthma during pregnancy, strategies that are culturally appropriate and target current and ex-smokers are needed. Special

attention is also needed for young mothers, women who already have children and women (re)initiating ICS treatment during pregnancy. In addition, we need to explore the influence of beliefs about medications and mental health on ICS adherence during pregnancy.

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TABLE E1. Crude and adjusted odds of nonadherence to inhaled corticosteroids in at baseline pregnancy among women with asthma—sensitivity analysis

	ICS at best	
Variable	Adjusted* OR 95% CI	*P* value
Ethnic identity		
Caucasian	Reference	
Indigenous	2.70 (0.99-7.38)	.052
Non-Caucasian/non-Indigenous	1.74 (0.83-3.65)	.144
Adult diagnosis	1.80 (0.92-3.52)	.085
Trigger—work	1.86 (0.99-3.48)	.053
Trigger—food	0.71 (0.42-1.20)	.202
ICS use at best	**0.29 (0.18-0.47)**	**<.001**
FEV_1% predicted (per %)	**0.98 (0.96-0.99)**	**.004**

CI, Confidence interval; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *OR*, odds ratio.
Bold values indicate significant results.
*Adjusted for all other variables in model.

TABLE E2. Crude and adjusted odds of persistent nonadherence to inhaled corticosteroids during pregnancy among women with asthma

	ICS at best		EPDS score	
Variable	Adjusted* OR 95% CI	*P* value	Adjusted* OR 95% CI	*P* value
ICS treatment at baseline				
No use	Reference		Reference	
Adherent	**0.25 (0.11-0.59)**	**.001**	**0.23 (0.13-0.43)**	**<.001**
Nonadherent	1.26 (0.63-2.51)	.517	0.63 (0.34-1.15)	.131
Smoking status				
Never	Reference			
Ex-smoker	1.46 (0.79-2.68)	.222		
Current smoker	**2.28 (1.09-4.80)**	**.029**		
Employed	0.70 (0.39-1.24)	.219		
Body mass index (kg/m^2)	1.03 (1.00-1.06)	.133		
ICS at best	0.54 (0.28-1.06)	.075		
Age (y)			**0.94 (0.90-0.99)**	**.016**
Parity			1.22 (0.97-1.53)	.085
EPDS score			**1.06 (1.01-1.11)**	**.012**

CI, Confidence interval; *EPDS*, Edinburgh Postnatal Depression Score; *ICS*, inhaled corticosteroid; *OR*, odds ratio.
Bold values indicate significant results.
*Adjusted for all other variables in model.