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Factors associated with non-adherence to inhaled corticosteroids for asthma during pregnancy

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Conflict of Interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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Abstract

Background: Non-adherence is common among pregnant women prescribed inhaled corticosteroids (ICS) for asthma, and may have serious consequences for mother and baby. Factors associated with ICS non-adherence have not been determined in this population.

Objectives: To determine factors associated with 1) non-adherence to ICS in early-mid pregnancy (cross-sectional) and 2) persistent non-adherence to ICS during pregnancy (longitudinal).

Methods: Data utilised come from three prospective studies (2004-2019) involving women with asthma recruited by 23 weeks gestation (N=1,614). 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. Non-adherence was defined as $\geq 20\%$ of prescribed dosages missed in the past week (baseline) and on at least two occasions during follow-up (persistent). Factors associated with ICS non-adherence were examined using backward stepwise logistic regression.

Results: Of 610 (38%) women prescribed ICS at baseline, 236 (39%) were classified as non-adherent. Of 612 (38%) women prescribed ICS during at least two follow-up visits, 149 (24%) were classified as persistent non-adherent. Factors associated with non-adherence at baseline were current or ex-smoking, non-Caucasian/non-Indigenous ethnicity, adult diagnosis of asthma, and lower lung function. Factors associated with persistent non-adherence 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 non-adherent to ICS during pregnancy. Strategies to improve ICS non-adherence should address maternal smoking and target women who (re-)initiate ICS use in pregnancy.

Highlights Box:***What is already known about this topic?***

Non-adherence 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 non-adherence 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 non-adherent to inhaled corticosteroids during pregnancy, which may assist healthcare professionals initiate a more targeted conversation with pregnant women about their asthma medication.

Keywords :

pregnancy, asthma, smoking, prospective studies, spirometry

Abbreviations used:

ACQ Asthma Control Questionnaire, BDP beclomethasone dipropionate, BMI Body Mass Index, EPDS Edinburgh Postnatal Depression Scale, ED Emergency Department, FEV₁ Forced Expiratory Volume in 1 second, FVC Forced Vital Capacity, F_ENO Fraction Exhaled Nitric Oxide, ICS Inhaled Corticosteroids, LABA Long-acting beta-agonist, OR Odds Ratio, OCS Oral Corticosteroids, RCT Randomised Controlled Trial, ROC Receiver operating curve, SABA Short-acting beta-agonists, SES Socio-Economic Status, URTI Upper Respiratory Tract Infection, WAP Written Action Plan

Introduction

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 (OCS) 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 beta-agonists (SABA) as reliever medication.⁷ However, medication non-adherence during pregnancy is a significant clinical problem,⁸ including rates as high as 40% of women with asthma.⁹ Studies examining non-adherence to asthma medication in pregnancy are limited,¹⁰⁻¹⁴ and factors associated with ICS non-adherence during pregnancy are largely unknown.

A systematic review reporting on asthma inhaler adherence among non-pregnant adults found that stronger beliefs about treatment necessity was 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 non-adherence varied and included self-report adherence, adherence questionnaires, canister weighing, electronic monitoring, and prescription refill records. Therefore, a meta-analysis of this data was not conducted.

ICS non-adherence 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 non-adherence unique to this population that need to be examined.

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

Methods

Population

Data come from three prospective cohorts of pregnant women with asthma recruited between July 2004 and June 2019 via seven 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 17-23 weeks' gestation from the John Hunter Hospital (Newcastle, NSW).³

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

Cohort 3 was an RCT of asthma treatment adjustment with F_ENO-based management vs usual care between March 2013 and June 2019, the *Breathing for Life Trial* (BLT).¹⁹ Women with asthma were recruited between 12-23 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 prior to participation.

Measurements

Baseline data from all three cohorts included maternal age, body mass index (BMI, kg/m²), 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 healthcare utilisation in past two years), asthma triggers (season, reflux, exercise, upper respiratory tract infection, work, pets, food, aspirin and fumes), and current asthma symptoms and medication use. Socio-economic status (SES) 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 categorised as 'No ICS at best' (ICS dose at best reported as zero) and 'ICS at best' (ICS dose >0µg/day at best reported). Forced expiratory volume in 1 second (FEV₁) 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 AU) and age- and height-adjusted percent predicted FEV₁ 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, Duernten, Switzerland), and only in those randomised 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 randomised to the control group in cohort 3, with uncontrolled asthma defined as ACQ score ≥1.5.²³ Additionally, asthma control was categorised 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 Scale²⁵ (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 assessment²⁶).

Statistical Analysis

All data were analysed using Stata IC version 15 (StataCorp College Station, TX, USA). At baseline, women were classified as non-adherent if they had missed $\geq 20\%$ of their prescribed ICS doses in the past week.¹¹ For the persistent non-adherence analysis, we included women who had at least two follow-up visits during pregnancy where ICS adherence data were collected. Persistent non-adherence during pregnancy was defined as being non-adherent (based on aforementioned definition) at two or more follow-up visits, where ICS was prescribed, during pregnancy (i.e. excluding the baseline visit).

Data were presented as mean $\pm$ standard deviation (SD), median [interquartile range, IQR] or n/N (%) unless otherwise stated. Continuous variables were compared between adherent and non-adherent women using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test as appropriate. Dichotomous variables were analysed using Chi-squared tests. The statistical significance threshold was set at the 0.05 level. Factors that may be associated with baseline non-adherence and persistent non-adherence ($p \leq 0.2$) were explored with backwards stepwise logistic regression models and expressed as Odds Ratios (OR) for the crude analyses and adjusted ORs (aOR) for the final model. We used the Aikake Information Criteria (AIC) and the Bayesian Information Criteria (BIC) to identify the best fitting models. Goodness of fit of the final models was assessed using the Hosmer-Lemeshow Chi-squared test with 10 subgroups, where $p > 0.05$ indicated a

satisfactory model. The area under the receiver operating curve (ROC) was determined for the best fitting model. Due to anticipated missing data for potentially important factors associated with non-adherence, 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 non-adherence

In total, 1,614 women were included from the three cohorts, of which 610 (38%) were prescribed ICS at baseline (approx. 19 weeks' gestation). Among these women, 236 (39%) were non-adherent 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 non-adherent group were more likely to use ICS/LABA combination therapy ($p=0.01$), more likely to have been diagnosed with asthma as an adult ($p<0.01$), and more likely to smoke ($p=0.01$), compared to women in the adherent group. Non-adherent women had a lower FEV₁% predicted ($p=0.02$), and higher F_ENO levels ($p=0.01$) compared to adherent women. Asthma control status did not differ between adherent and non-adherent women, whether based on GINA guidelines ($p=0.27$) or ACQ ($p=0.46$).

Table 1

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 (ED) visits for asthma and FEV₁% predicted. **Table 2** For the adjusted model, the area under the ROC curve was 67% (95%CI 62-72%), the goodness of fit test had a p-value of 0.24. Current smokers and non-Caucasian/non-Indigenous women were 2.1 times more likely to be non-adherent compared to never smokers and Caucasian women respectively. Ex-smokers were 71%

more likely to be non-adherent than never smokers. Women diagnosed with asthma as an adult were almost twice as likely to be non-adherent compared to women diagnosed in childhood. A higher FEV₁% predicted reduced the odds of being non-adherent by 10% for each 5% increase of FEV₁% 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 non-adherent. The final model additionally included ethnic identity, adult diagnosis, work and food as an asthma trigger, and FEV₁% predicted. **Table E1** The area under the ROC curve was 71% (95%CI 65-76%), the goodness of fit test had a p-value of 0.67.

Persistent non-adherence

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

Persistent non-adherence to ICS was associated with smoking at baseline (p=0.03) and unemployment (p=0.02). Persistently non-adherent women were more likely to have uncontrolled asthma at baseline compared to adherent women (GINA p=0.02 or ACQ p<0.01). **Table 3** Women prescribed ICS medication at baseline were less likely to be non-adherent during pregnancy compared to women who were not prescribed ICS at baseline (p<0.01). Furthermore, women who were non-adherent to prescribed ICS treatment at baseline were more likely to remain non-adherent throughout pregnancy compared to women who were adherent at baseline (p<0.01). **Figure 3**

The multivariate model for the persistent non-adherence analysis included maternal age, ICS treatment at baseline, and parity. **Table 4** The area under the ROC curve was 67% (95%CI 63-72%),

the goodness of fit test had a p-value of 0.66. Compared to non-ICS users at baseline, women who were ICS adherent at baseline were 72% less likely to be persistently non-adherent. Furthermore, increased parity increased the odds of persistent non-adherence by 24% per viable pregnancy. In contrast, increasing maternal age was associated with a 5% reduced odds of persistent non-adherence 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 non-adherent during pregnancy than women who reported not to use ICS 'at best'. The area under the ROC curve was 74% (95%CI 68-79%), and the goodness-of-fit had a p-value of 0.70. **Table E2**

In the second sensitivity analysis for persistent non-adherence, 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 non-adherence with the inclusion of the EPDS score. With each point increase in EPDS score, women were 6% more likely to be persistently non-adherent. The area under the ROC curve was 68% (95%CI 63-74%) and the goodness-of-fit had a p-value of 0.70. **Table E2**

Discussion

This is the first study to report clinical characteristics associated with ICS non-adherence in women with asthma during pregnancy, of whom 39% were non-adherent to their prescribed ICS treatment at baseline (~19 weeks' gestation), and 24% were persistently non-adherent throughout pregnancy, despite follow-up visits which included asthma education.¹¹ Factors associated with non-adherence at baseline were non-Caucasian/non-Indigenous ethnicity, current or ex-smoking status, being

diagnosed with asthma as an adult, and a lower FEV₁%. Factors associated with persistent non-adherence 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 non-adherence 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 utilised a commonly used value of 20% missed doses to determine ICS non-adherence. In the systematic review of Dima et al. 12 studies (where all but one used objective measures), reported cut-off values for non-adherence (ranging from 15-50%) with half of them using the 20% cut-off.¹⁵ Previous research in children with asthma linked this level of non-adherence with worse asthma control.²⁷ Interestingly, we did not observe a difference in asthma control status between the adherent and non-adherent groups, as might be expected. This might be due to the simultaneous measurement of non-adherence and asthma control. Williams et al. reported that adults with ICS non-adherence of <25% experienced the primary treatment benefit e.g. prevention of exacerbations.²⁸ The 20% cut-off may be a good balance between realistic patient behaviour (missing 20% of weekly dosages approximates missing one daily dose of asthma medication per week) and clinical efficacy; however, pharmacoepidemiological evidence for this cut-off value is still needed.

The current literature does not have a definition for persistent non-adherence. Grzeskowiak et al. defined persistent uncontrolled asthma during pregnancy as having an ACQ6 $\geq$ 1.5 at two or more visits during pregnancy (8 weeks apart).²⁹ We defined persistent non-adherence as being non-adherent at two or more visits four to six weeks apart, which corresponds closely with recommendation for monthly asthma assessment during pregnancy.²⁴ 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 healthcare providers to

identify women who are non-adherent and institute interventions, including providing education on the importance of medication use.

Our results show a significantly increased risk of non-adherence 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 behaviours such as medication adherence. Our results also show that women with a non-Caucasian/non-Indigenous ethnicity were more likely to be non-adherent compared to 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 non-adherence 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 which 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 to women who did not use ICS at baseline. This is consistent with previous research, which has shown that past medication behaviour 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 prior to enrollment. This decision is often made by the woman herself without consulting a physician.^{34,35} These women may have specific medication beliefs which 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 healthcare 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 non-adherent during pregnancy. Younger women may have more social barriers³⁸ than older women, which may contribute to medication non-adherence. In contrast to the reduced risk for older women, women who already have a child were also at increased risk of persistent non-adherence. The reasons for this are unknown.

In our sensitivity analyses we found two 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 non-adherence.^{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 medication⁴⁰ 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 prior to pregnancy. Given that asthma is a dynamic disease, asthma control and need for ICS medication may change over time.

Additionally, women with higher EPDS scores were at increased odds of persistent non-adherence. Mental health problems have previously been found to be associated with ICS non-adherence 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 to 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 non-adherent.

This study has several strengths. Firstly, 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 three 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 three cohorts were combined to identify clinical factors related to non-adherence. 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 non-adherence. This could have led to social desirability bias, resulting in the level of non-adherence 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 to outside of pregnancy.¹² Furthermore, we may have underestimated ICS non-adherence 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 non-adherent. Also, we may have underestimated complete non-adherence (e.g. women who stopped using ICS in early pregnancy, even when needed). We did not assign asthma phenotypes to the women in this study, and women with T2-low asthma may have a different response to ICS medications⁴⁵ which could

impact adherence. Other factors which may be associated with non-adherence, 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 non-adherence 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 non-adherence during pregnancy on asthma- and pregnancy-related health outcomes for the mother and infant. For healthcare providers managing women with asthma during pregnancy, it is important to identify risk factors for ICS non-adherence 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. Additionally, we need to explore the influence of beliefs about medications and mental health on ICS adherence during pregnancy.

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Figure legend**Figure 1.** Study population flow diagram**Figure 2.** Adjusted Odds Ratios for inhaled corticosteroid (ICS) non-adherence at baseline.**Figure 3.** Adjusted Odds Ratios for persistent inhaled corticosteroid (ICS) non-adherence during pregnancy.**Tables**

Table 1. Baseline characteristics of women with asthma, classified as adherent vs. non-adherent to inhaled corticosteroids, at baseline.

	Adherent (n=374)	Non-Adherent (n=236)	p-value
Clinical Trial, n (%)			0.48
Cohort 1	22 (6)	14 (6)	
Cohort 2	53 (14)	42 (18)	
Cohort 3	299 (80)	180 (76)	
Maternal demographics			
Age, years	30.6 ± 5.3	30.8 ± 5.6	0.62
Gestational age at recruitment	18.6 [16.3, 20.9]	18.8 [16.3, 20.6]	0.81
BMI (kg/m ²)	27.1 [24.0, 32.8] n=370	26.8 [23.6, 33.1] n=235	0.32
BMI categories, n/N (%)			0.36
Non-overweight [<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 (%)			<0.01
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)	0.84
Ethnicity, n/N (%)			0.03
Caucasian	305/347 (88)	173/217 (80)	
Indigenous	14/347 (4)	14/217 (6)	

Non-Caucasian/Non-Indigenous*	28/347 (8)	30/217 (14)	
Socio-economic Indexes for Areas quintiles, n(%)			0.97
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	0.49
Parity, n	0 [0, 1] n=365	1 [0, 2] n=230	0.13
Multiparous, n/N (%)	181/365 (50)	126/230 (55)	0.22
Prenatal EPDS Score	5 [2, 9] n=211	5 [2, 9] n=135	0.93
Asthma-related			
<i>Asthma History</i>			
Age at diagnosis, years	4.5 [2.0, 9.0] n=361	6.0 [2.0, 13.0] n=228	0.03
Adult diagnosis (≥ 18 years), n/N (%)	36/361 (10)	41/228 (18)	<0.01
≥ 1 Hospitalisation in past 2 years, n/N (%)	26/371 (7)	14/235 (6)	0.63
≥ 1 ED visit in past 2 years, n/N (%)	59/371 (16)	27/235 (12)	0.14
≥ 1 OCS course in past 2 years, n/N (%)	104/371 (28)	59/234 (25)	0.45
ICS use 'at best', n/N (%)	233/307 (76)	94/183 (51)	<0.01
Triggers, n/N (%)			
Season	325/373 (87)	214/235 (91)	0.14
Reflux	53/374 (14)	33/235 (14)	0.96
Exercise	289/374 (77)	184/235 (78)	0.77
URTI	333/373 (89)	207/235 (88)	0.65
Work	50/374 (13)	46/235 (20)	0.04
Pets	181/374 (48)	103/235 (44)	0.27
Food	119/374 (32)	57/235 (24)	0.05
Aspirin	24/374 (6)	8/235 (3)	0.10
Fumes	252/374 (67)	157/235 (67)	0.88
<i>Current Asthma Symptoms</i>			
ACQ score	1.29 [0.71, 2.14] n=237	1.43 [0.71, 2.18] n=142	0.61
Uncontrolled Asthma (ACQ ≥ 1.5), n/N (%)	106/237 (45)	69/142 (49)	0.46
<i>GINA Control status</i>			0.27
Well controlled	72/370 (20)	34/233 (15)	
Partly controlled	147/370 (40)	103/233 (44)	
Uncontrolled	151/370 (41)	96/233 (41)	
<i>Lung Function</i>			
FEV ₁ % predicted	91.8 [81.4, 99.9] n=323	87.7 [77.6, 98.2] n=211	0.02
FVC % predicted	94.5 [86.5, 103.2] n=321	92.7 [83.2, 102.6] n=208	0.18
FEV1:FVC ratio (%)	81.3 [76.1, 85.1] n=321	79.6 [73.8, 84.8] n=208	0.03
FeNO (ppb)	14.4 [9.2, 25.0] n=224	19.6 [11.0, 33.0] n=132	0.01
<i>Asthma Medications</i>			

ICS/LABA combination (n, %)	272 (73)	192 (81)	0.01
BDP equivalent ICS dose ($\mu\text{g}/\text{day}$)	400 [250, 800] n=369	400 [250, 800] n=229	0.84
Reliever use in the past week (times)	4 [1, 12] n=367	4 [0, 8] n=232	0.43
<i>Asthma Self-management skills, n/N (%)</i>			
Correct reliever knowledge	128/338 (38)	73/213 (34)	0.39
Correct controller knowledge	97/338 (29)	47/212 (22)	0.09
Optimal pMDI technique	108/312 (35)	69/202 (34)	0.92
Optimal turbuhaler technique	103/297 (35)	66/180 (37)	0.66
WAP possession	93/369 (25)	56/233 (24)	0.71
Data presented as n/N (%) for categorical variables with missing data, n (%) for categorical variables without missing data, median [interquartile range or mean $\pm$ sd]; Percentages may add up over or not up to 100% due to rounding. Abbreviations: ACQ Asthma Control Questionnaire, BDP Beclomethasone dipropionate, BMI Body Mass Index, ECO Exhaled Carbon Monoxide, ED Emergency Department, EPDS Edinburgh Postnatal Depression Score, FeNO Fractional exhaled Nitric Oxide, FEV₁ Forced Expiratory Volume in 1 second, FVC Forced Vital Capacity, ICS Inhaled Corticosteroids, LABA Long-acting beta-agonist, OCS Oral Corticosteroids, pMDI pressurised Metered Dose Inhaler, SES Socio-Economic Status, URTI Upper Respiratory Tract Infection, WAP Written Action Plan *Non-Caucasian/Non-Indigenous ethnicity includes African, Asian, South American, Middle Eastern, Pacific Islander and Maori			

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Table 2. Crude and adjusted odds of non-adherence 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				
<i>Never</i>	Reference		Reference	
<i>Ex</i>	1.37 (0.95-1.99)	0.097	1.71 (1.09-2.67)	0.019
<i>Current</i>	2.64 (1.53-4.56)	<0.001	2.13 (1.10-4.11)	0.025
Ethnic Identity				
<i>Caucasian</i>	Reference		Reference	
<i>Indigenous</i>	1.76 (0.82-3.78)	0.146	1.67 (0.67-4.16)	0.268
<i>Non-Caucasian/Non-Indigenous</i>	1.89 (1.09-3.27)	0.023	2.16 (1.08-4.29)	0.029
ED visit in past 2 years	0.69 (0.42-1.13)	0.139	0.57 (0.30-1.09)	0.091
Adult diagnosis	1.98 (1.22-3.21)	0.006	1.97 (1.10-3.53)	0.022
Trigger – Work	1.58 (1.02-2.45)	0.042	1.59 (0.92-2.75)	0.095
Trigger - Food	0.69 (0.47-0.99)	0.046	0.65 (0.41-1.03)	0.069
Trigger - Aspirin	0.51 (0.23-1.16)	0.110	0.37 (0.12-1.16)	0.090
FEV1% predicted (per %)	0.99 (0.97-1.00)	0.022	0.98 (0.97-1.00)	0.029
ICS/LABA combination use	1.64 (1.10-2.44)	0.016	1.59 (0.97-2.61)	0.068
*Adjusted for all other variables in model; Abbreviations used: ED Emergency Department, FEV1 Forced Expiratory Volume in 1 second, ICS Inhaled Corticosteroids, LABA Long-acting beta-agonist				

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Table 3. Baseline characteristics of women with asthma, classified as adherent vs. persistently non-adherent to inhaled corticosteroids during pregnancy.

	Adherent (n=463)	Persistent Non-Adherent	p-value
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		(n=149)	
Clinical Trial, n (%)			0.09
Cohort 1	30 (7)	4 (3)	
Cohort 2	125 (27)	50 (34)	
Cohort 3	308 (67)	95 (64)	
Maternal demographics			
Age (years)	29.9 (5.4)	28.8 (5.6)	0.02
Gestational age at recruitment	18.0 [15.6, 20.4]	18.1 [15.6, 19.9]	0.32
BMI (kg/m ²)	27.5 [23.9, 33.4]	29.0 [24.2, 32.9]	0.20
BMI categories, n (%)			0.34
Non-overweight [<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 (%)			0.02
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)	0.02
Ethnicity, n/N (%)			0.84
Caucasian	378/436 (87)	115/135 (85)	
Indigenous	26/436 (6)	8/135 (6)	
Non-Caucasian/Non-Indigenous*	32/436 (7)	12/135 (9)	
Socio-economic Indexes for Areas quintiles, n(%)			0.10
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]	0.02
Parity, n	1 [0, 1] n=460	1 [0, 2]	0.07
Multiparous, n/N (%)	238/460 (52)	89 (60)	0.09
Prenatal EPDS Score	5.0 [2.0, 8.8] n=296	6.0 [4.0, 10.0]	0.02
Asthma-related			
Asthma History			
Age at diagnosis (years)	5.0 [2.0, 12.0] n=448	5.0 [3.0, 13.0] n=144	0.62
Adult diagnosis (≥18 years)	59/448 (13)	22/144 (15)	0.52
≥1 Hospitalisation in past 2 years, n/N (%)	25/460 (5)	6 (4)	0.50
≥1 ED visit in past 2 years, n/N (%)	60/460 (13)	19 (13)	0.93
≥1 OCS course in past 2 years, n/N (%)	104/460 (23)	27 (18)	0.25
ICS use 'at best' (n, %)	165/315 (52)	28/90 (31)	<0.01
Triggers, n/N (%)			
Season	414/462 (90)	132 (89)	0.73
Reflux	62/462 (13)	18/148 (12)	0.74
Exercise	376 (81)	123 (83)	0.71
URTI	414 (89)	132 (89)	0.78

Work	87 (19)	24 (16)	0.49
Pets	202 (44)	64 (43)	0.87
Food	120 (26)	46 (31)	0.22
Aspirin	22 (5)	8/148 (5)	0.75
Fumes	339 (73)	105 (71)	0.52
<i>Current Asthma Symptoms</i>			
ACQ score	1.31 [0.71, 2.14] n=462	1.71 [1.00, 2.29]	<0.01
Uncontrolled Asthma (ACQ $\geq$ 1.5), n/N (%)	210/462 (46)	90 (60)	<0.01
<i>GINA Control status, n/N (%)</i>			0.02
Well controlled	89/459 (19)	16/147 (11)	
Partly controlled	194/459 (42)	58/147 (40)	
Uncontrolled	176/459 (38)	73/147 (50)	
<i>Lung Function</i>			
FEV ₁ % predicted	89.6 [80.6, 98.5] n=401	88.4 [79.9, 98.4] n=129	0.58
FVC % predicted	93.9 [84.8, 103.1] n=400	94.47 [86.9, 102.3] n=127	0.95
FEV ₁ :FVC %	81.2 [75.4, 85.0] n=399	80.7 [74.0, 86.0] n=127	0.83
FeNO (ppb)	19.0 [11.0, 36.9] n=445	17.0 [8.0, 35.0] n=144	0.05
<i>Medication use at baseline</i>			
ICS	276 (60)	58 (39)	<0.01
ICS/LABA combination, n/N (%)	213/276 (77)	42/58 (72)	0.43
ICS dose (BDP equivalent, µg/day)	400 [250, 800] n=269	800 [363, 800] n=58	0.02
ICS treatment at baseline, n/N (%)			<0.01
Non User	187/455 (41)	91/148 (62)	
Adherent	186/455 (41)	23/148 (16)	
Non-Adherent	82/455 (18)	34/148 (23)	
Reliever use in the past week (times)	4 [0, 8] n=456	4 [0, 7] n=146	0.72
<i>Self-management skills, n/N (%)</i>			
Correct reliever knowledge	125/416 (30)	28/132 (21)	0.05
Correct controller knowledge	66/319 (21)	15/91 (17)	0.39
Optimal pMDI technique	124/410 (30)	34/133 (26)	0.32
Optimal Turbuhaler technique	107/330 (32)	27/102 (27)	0.26
WAP possession	105/458 (23)	25/147 (17)	0.13
Data presented as n/N (%) for categorical variables with missing data, n (%) for categorical variables without missing data, median [interquartile range or mean $\pm$ sd]; Percentages may add up over or not up to 100% due to rounding. Abbreviations: FACQ Asthma Control Questionnaire, BDP Beclomethasone dipropionate, BMI Body Mass Index, ECO Exhaled Carbon Monoxide, ED Emergency Department, EPDS Edinburgh Postnatal Depression Score, FeNO Fractional exhaled Nitric Oxide, FEV ₁ Forced Expiratory Volume in 1 second, FVC Forced Vital Capacity, ICS Inhaled Corticosteroids, LABA Long-acting beta-agonist, OCS Oral Corticosteroids, pMDI pressurised Metered Dose Inhaler, SES Socio-Economic Status, URTI Upper Respiratory Tract Infection, WAP			

Written Action Plan

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

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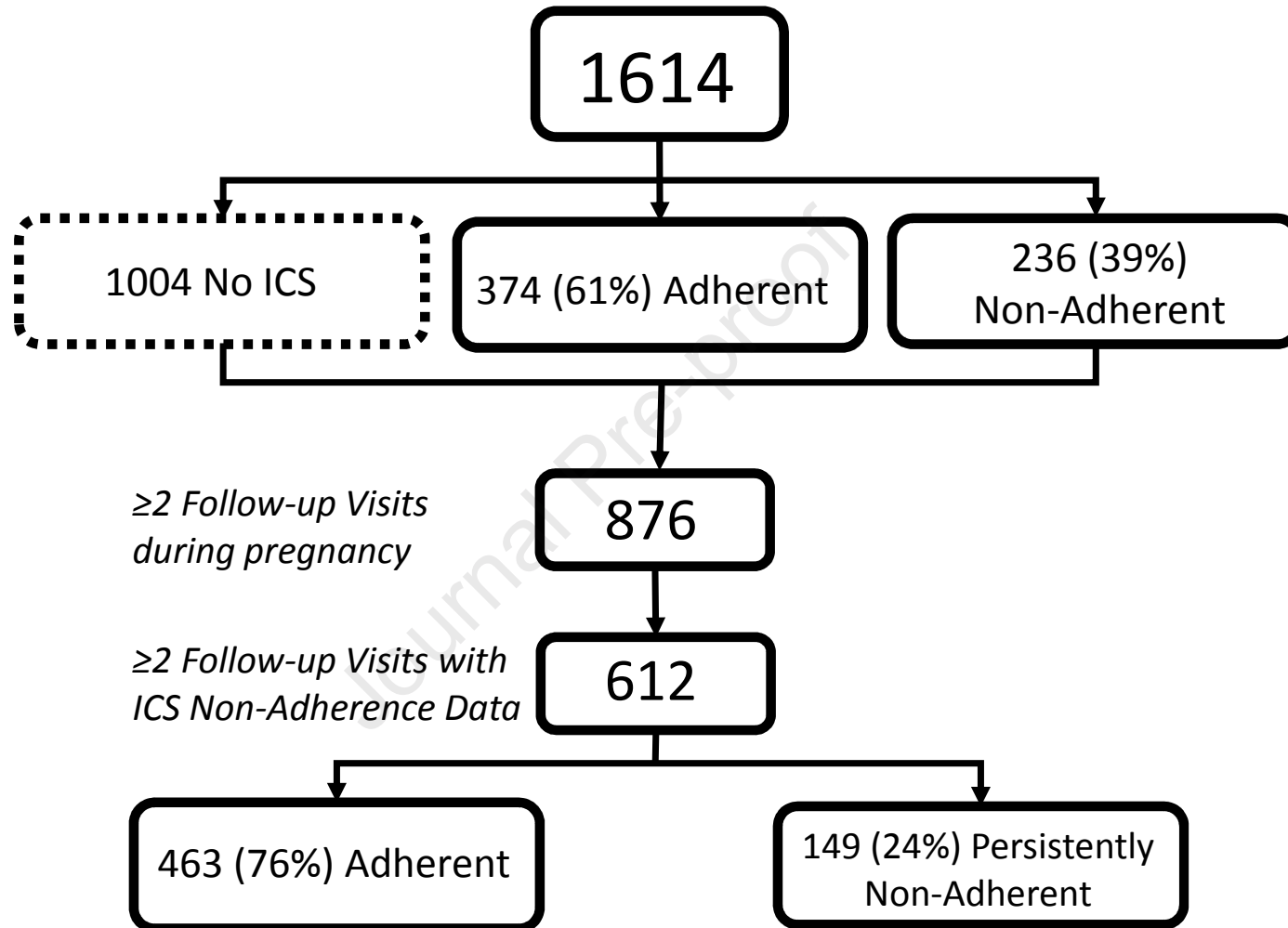
Table 4. Crude and adjusted odds of persistent non-adherence to inhaled corticosteroids during pregnancy among women with asthma

Variable	Crude OR 95% CI	P-value	Adjusted* OR 95% CI	P-value
ICS Treatment at baseline				
<i>No use</i>	Reference		Reference	
<i>Adherent</i>	0.25 (0.15-0.42)	<0.001	0.28 (0.17-0.46)	<0.001
<i>Non-adherent</i>	0.85 (0.53-1.37)	0.506	0.92 (0.57-1.49)	0.740
Age (year)	0.96 (0.93-1.00)	0.025	0.95 (0.92-0.99)	0.015
Parity (n)	1.18 (1.00-1.39)	0.048	1.24 (1.03-1.49)	0.023
*Adjusted for all other variables in model. Abbreviations used: ICS Inhaled Corticosteroids.				

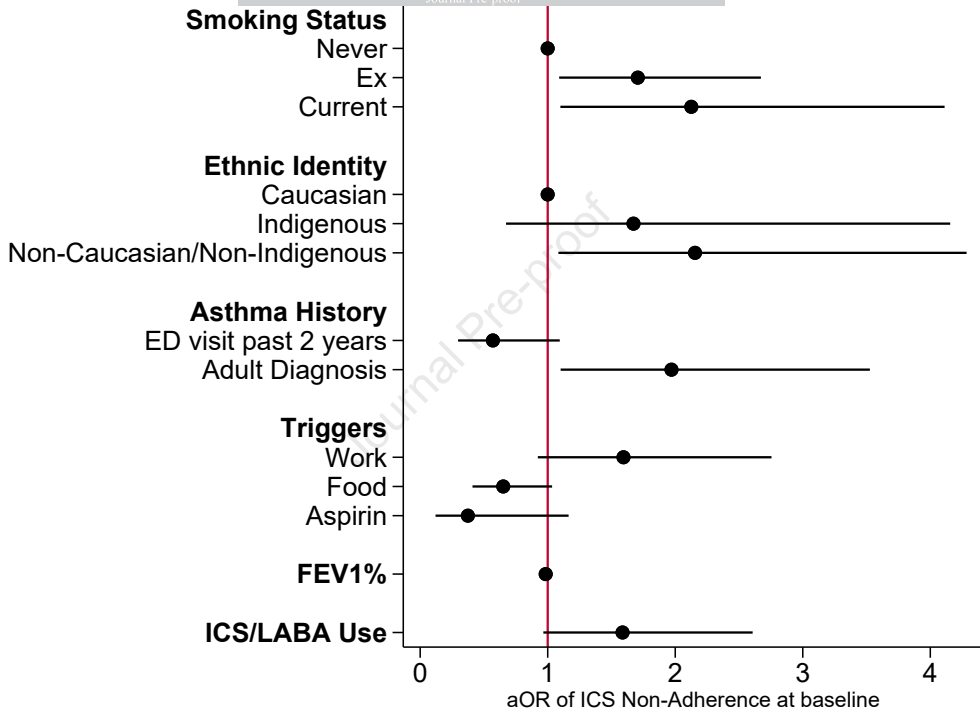
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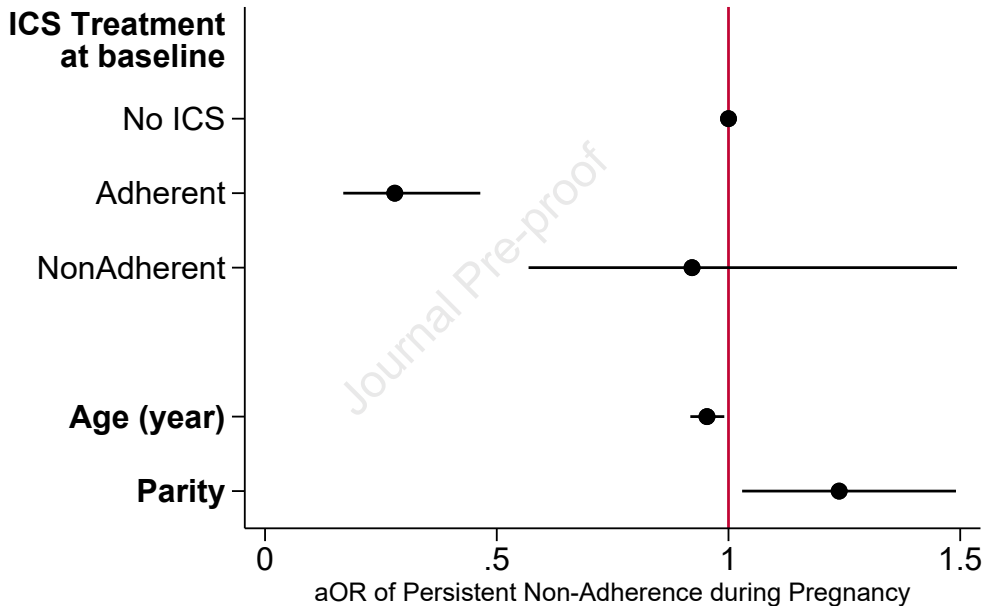
*Pregnant women with
asthma recruited
(~19 weeks gestation)*

*Baseline ICS Non-
Adherence Analysis*



*Persistent ICS Non-
Adherence Analysis*





Factors associated with non-adherence to inhaled corticosteroids for asthma during pregnancy

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Table E1. Crude and adjusted odds of non-adherence 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		
<i>Caucasian</i>	Reference	
<i>Indigenous</i>	2.70 (0.99-7.38)	0.052
<i>Non-Caucasian/Non-Indigenous</i>	1.74 (0.83-3.65)	0.144
Adult diagnosis	1.80 (0.92-3.52)	0.085
Trigger – Work	1.86 (0.99-3.48)	0.053
Trigger - Food	0.71 (0.42-1.20)	0.202
ICS use at best	0.29 (0.18-0.47)	<0.001
FEV1% predicted (per %)	0.98 (0.96-0.99)	0.004
*Adjusted for all other variables in model; Abbreviations used: FEV1 Forced Expiratory Volume in 1 second, ICS Inhaled Corticosteroids, LABA Long-acting beta-agonist		

Table E2. Crude and adjusted odds of persistent non-adherence 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				
<i>No use</i>	Reference		Reference	
<i>Adherent</i>	0.25 (0.11-0.59)	0.001	0.23 (0.13-0.43)	<0.001
<i>Non-adherent</i>	1.26 (0.63-2.51)	0.517	0.63 (0.34-1.15)	0.131
Smoking status				
<i>Never</i>	Reference			
<i>Ex-Smoker</i>	1.46 (0.79-2.68)	0.222		
<i>Current Smoker</i>	2.28 (1.09-4.80)	0.029		
Employed	0.70 (0.39-1.24)	0.219		
Body Mass Index (kg/m2)	1.03 (1.00-1.06)	0.133		
ICS at best	0.54 (0.28-1.06)	0.075		
Age (year)			0.94 (0.90-0.99)	0.016
Parity			1.22 (0.97-1.53)	0.085
EPDS score			1.06 (1.01-1.11)	0.012
*Adjusted for all other variables in model. Abbreviations used: ICS Inhaled Corticosteroids.				