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Asthma Control and Mental Health During Pregnancy

Impact of a History of Maternal Depression and Anxiety on Asthma Control During Pregnancy

Grzeskowiak, Luke E^{1,2}, Smith, Brian³, Roy, Anil³, Schubert K. Oliver⁴, Baune, Bernhard T⁴, Dekker, Gustaaf A¹, Clifton, Vicki L^{1,5}

¹Robinson Research Institute, School of Medicine, University of Adelaide, Adelaide, Australia

²SA Pharmacy, Pharmacy Department, Flinders Medical Centre, Adelaide, Australia

³Respiratory Medicine Unit, The Queen Elizabeth Hospital, Adelaide, Australia

⁴Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia

⁵Mater Medical Research Institute, University of Queensland, Brisbane, Australia

Corresponding Author: Professor Vicki L Clifton, Mater Medical Research Institute, Level 4, Translational Research Institute, 37 Kent St, Woolloongabba, Qld. 4101, Brisbane, Australia, Vicki.clifton@mater.uq.edu.au, Phone 617 3443 7640

Abstract

Objective: To determine the impact of self-reported maternal depression/anxiety on asthma control during pregnancy.

Method: Pregnant women with a doctor diagnosis of asthma (n=189) were prospectively recruited at their antenatal booking visit and the presence of maternal depression and anxiety was

identified using self-report and routine questionnaire assessments. Data on exacerbations and asthma control were collected during gestation. Asthma control was assessed using the Juniper asthma control questionnaire and women were classified as having recurrent uncontrolled asthma if their ACQ score was > 1.5 during two or more consecutive study visits. Exacerbations were defined as events that lead to increased treatment requirements, doctor or hospital visits.

Results: There were 85 women with self-reported depression/anxiety and 104 women without self-reported depression/anxiety. The presence of depression/anxiety was associated with an increased likelihood (adjusted HR 1.67: 95% CI 1.03-2.72), and incidence (adjusted IRR 1.71: 95% CI 1.13-2.58) of uncontrolled asthma during pregnancy, as well an increased risk of recurrent uncontrolled asthma during 2 or more study visits (adjusted RR 1.98: 95% CI 1.00-3.91). No impact of depression/anxiety was observed with respect to the likelihood (adjusted HR 0.70: 95% CI 0.35-1.41) or incidence of exacerbations during pregnancy (adjusted IRR 0.66: 95% CI 0.35-1.26).

Conclusions: This study provides evidence that the presence of maternal depression/anxiety is associated with an increased likelihood and incidence of uncontrolled asthma during pregnancy. Given the high prevalence of comorbid depression/anxiety among asthmatics, further research investigating such associations is urgently required.

Keywords

asthma, pregnancy, asthma control, depression, anxiety, mental health

Background

Asthma is one of the most prevalent chronic medical conditions reported during pregnancy, with a prevalence of between 8-13% worldwide.^{1, 2,3} The presence of maternal asthma is associated with poor perinatal outcomes, which include increased risk of low birth weight (RR 1.46; 95%CI 1.22-1.75), small-for-gestational age (RR 1.22; 1.14-1.31) and preterm birth (RR 1.41; 1.22-1.61). In addition, mothers with asthma are at greater risk of developing pre-eclampsia (RR 1.54; 1.32-1.81), gestational diabetes (RR 1.39; 1.17-1.66) and Caesarean section (RR 1.31; 1.22-1.39).^{4, 5} While not well investigated, poor perinatal outcomes are likely related to impaired asthma control during pregnancy⁶.

The management of asthma during pregnancy is recognized as a major challenge as the course of asthma severity and its treatment can change significantly with pregnancy, which in turn can affect pregnancy outcomes.⁷ International guidelines are consistent in their recommendations that asthma be managed during pregnancy in the same manner as a non-pregnant adult. This includes using the same asthma medications and assessing asthma control and adjusting inhaled medications accordingly at regular intervals during pregnancy. Despite all efforts to improve asthma management during pregnancy, to date there has been no significant reduction in perinatal morbidity and mortality within the antenatal setting.⁷

An important factor for improving perinatal outcomes lies in the identification of risk factors of poor asthma control. Mental illness is a well-recognised comorbidity among those with asthma, with evidence that anxiety, depression and panic disorders are more common among people with asthma than in the general population.⁸⁻¹⁰ The presence of a mental health illness occurs in around 15% of pregnancies¹¹, but this is noted to be much higher among socially disadvantaged

populations¹². This is of further importance as mental illness is associated with significant increased risk of poor perinatal outcomes similar to asthma¹³. Furthermore, previous studies involving non-pregnant adults have demonstrated a strong association between mental illness and impaired asthma control and increased risk of asthma exacerbations.^{8, 9, 14, 15} The impact of mental illness on asthma control during pregnancy, however, remains poorly examined to date, with limited data available from a recent Australian cohort of pregnant asthmatics suggesting that maternal anxiety is associated with impaired quality of life, poor asthma control and increased risk of asthma exacerbations during pregnancy.^{16, 17} In the current study we aimed to investigate the association between maternal self-reported depression and anxiety on asthma control and asthma exacerbations during pregnancy.

Methods

Subjects

This study was part of a larger prospective cohort study undertaken at the Lyell McEwin Hospital (LMH) that assessed the effects of asthma throughout pregnancy on the mother, placenta and baby¹⁸. The LMH is a tertiary teaching hospital in a socially disadvantaged area of northern Adelaide, South Australia. Recruitment and data collection for all mothers and babies began in May 2009 and ended in July 2013. Women with current asthma were recruited at their first booking visit (12- 20 weeks gestation).

Prospective asthma study and standard-care

Pregnant women with a doctor diagnosis of asthma (n=189) were recruited through the Lyell McEwin Hospital antenatal clinics (South Australia, Australia) between May 2009 and May

2012 to take part in a non-interventional prospective cohort study evaluating the impact of maternal asthma on perinatal outcomes.

Women were assessed by a midwife, who had completed additional respiratory training, at 12, 20, 28, and 36 weeks gestation. The midwife utilised a standardised data collection tool to collect demographic data including maternal weight, height, smoking status, previous obstetric history, medical history. In addition to demographic variables, data were collected to determine current asthma therapy and control, current asthma triggers, co-morbidities and past history including frequency of oral corticosteroid use and hospital admissions for asthma. Forced expiratory volume at one second (FEV1) and forced vital capacity (FVC) was measured by an Easy One spirometer before and after administration of salbutamol. FEV1% predicted was calculated based on the patient's age, ethnicity and height using the equations of Gore *et al.*³⁴ Data were prospectively collected on asthma medications (dose, frequency and duration across trimesters). The same midwife saw women for each of their respective visits. Patients assessed as unstable and requiring medical review were referred to their primary care physician or to a respiratory physician.

Assessment of maternal depression and anxiety

The presence of maternal depression or anxiety was identified based on maternal self-report of medical diagnoses as occurs as part of routine mental health screening assessments undertaken during antenatal care booking visits. Current depressive symptom severity was assessed at 12 weeks gestation using an Antenatal Risk Questionnaire (ANRQ)¹⁹ and Edinburgh Postnatal Depression Score Questionnaire (EPDS)²⁰. The ANRQ is a self-report psychosocial assessment

tool which aids in the prediction of women who are at risk of developing postnatal depression. The EPDS is a set of 10 screening questions to assess whether women have symptoms that are common with depression and anxiety during pregnancy and in the year following the birth of a child.

Asthma Outcome Evaluation

Asthma outcomes included the collection of data on asthma exacerbations and asthma control throughout pregnancy. Asthma control was directly assessed at each visit using the Juniper Asthma Control Questionnaire (ACQ). The ACQ is a 7-item validated questionnaire which covers asthma symptoms and lung function, with scores >1.5 indicative of uncontrolled asthma.¹¹ Episodes of uncontrolled asthma, or loss of control, between study visits were identified based on the requirement for increased medication use or increased asthma symptoms which were self-managed by the women and did not require additional medical intervention. An exacerbation event was defined as moderate/severe if it required a hospital admission, emergency department (ED) presentation, an unscheduled doctor visit, or a course of oral steroids due to asthma. Additional asthma outcomes included recurrent uncontrolled asthma, defined as an ACQ score greater than 1.5 during two or more study visits, and commencement of new ICS during pregnancy.

Additional covariates

Smoking status was defined as smokers (current smokers plus those who quit during pregnancy) and non-smokers (those who never smoked and those who quit before pregnancy). BMI was calculated based on maternal height and weight recorded at antenatal booking visit. Parity was

defined as either the participant's first pregnancy (parity=0) or at least the participant's second pregnancy (parity= 1+).

Maternal smoking was assessed by maternal self-report, with women classified according to smoking status during the first antenatal visit. Socioeconomic status for each woman was determined using her residential postcode at the time of delivery. Women were then ranked according to their level of advantage, or relative disadvantage, based on data from the Socio-Economic Indexes for Areas, calculated from the Australian Bureau of Statistics' 5-yearly Census of Population and Housing. These indexes are widely used measures of relative socioeconomic status.²¹

Statistical Analysis

Differences between study groups were evaluated using independent t-tests for parametric continuous variables, Mann-Whitney U test for non-parametric variables, and Chi-Square test for categorical variables.

The likelihood of asthma exacerbations or uncontrolled asthma occurring during pregnancy was evaluated using a Cox proportional-hazards regression, with resulting hazard ratios (HR) and 95% confidence intervals (CIs). The incidence of asthma exacerbations and uncontrolled asthma were compared between the two groups using Poisson regression with robust variance estimates, with resulting Incidence Rate Ratios (IRR) and 95% CIs. This model took into account the amount of time each woman was followed up during the study. The prevalence of recurrent uncontrolled asthma was compared between the two groups using a generalised linear model (Poisson distribution) with robust variance estimates, with resulting relative risks (RR) and

95%CIs. Each of the models were adjusted for potential confounders including maternal smoking, BMI, age, parity, and baseline ICS use. In addition, to account for potential bias due to study attrition (i.e. missing follow-up data) we utilised inverse probability weighting²². This involved using logistic regression (for completed all study visits versus lost to follow-up as outcome) to determine weights for each individual using the inverse probability of response²². Completion of all study visits was predicted based on maternal depression/anxiety, maternal smoking, BMI, age, parity, and baseline ICS use. The individual weighting factor for these covariates (their inverse probability) was used as a sample weighting adjustment in all regression models. All reported *P* values were two-tailed, and a *P* value of <0.05 was considered to be statistically significant. All statistical procedures were carried out using SPSS version 19 (SPSS Inc., Chicago, IL, USA).

Ethics Approval

Approval for the study was provided by the The Queen Elizabeth Hospital, Lyell McEwin Hospital, and Modbury Hospital Human Research Ethics Committee and The University of Adelaide Human Research Ethics Committee. All women provided written informed consent.

Results

The prospective cohort consisted of 189 asthmatic pregnant women, of which 85 had a history of depression/anxiety. The median age and BMI of both groups were similar, as was parity, ethnicity, smoking status, and baseline ICS use (Table 1). As expected, women with a history of depression/anxiety had higher ANRQ and EPDS scores recorded at the 12 week gestation

booking visit, with 20% of those with depression/anxiety reporting concurrent antidepressant medication use.

The likelihood of women experiencing uncontrolled asthma during at least one of the study visits was significantly higher among those women with a history of depression/anxiety (52.9% vs. 32.7%; $p=0.005$), as was the proportion of women who experienced recurrent uncontrolled asthma during 2 or more study visits (23.5% vs. 9.6%; $p=0.009$, Table 2). Following adjustment for potential confounders, the differences remained statistically significant, with an increased hazard ratio of 1.67 for uncontrolled asthma (95% CI 1.03-2.72) and 1.98 for recurrent uncontrolled asthma (95% CI 1.00-3.91) during pregnancy in women with a history of depression/anxiety (Table 3). Furthermore, the presence of a history of depression/anxiety was associated with a higher incidence of uncontrolled asthma during pregnancy (IRR 1.71; 95% CI 1.13-2.58). The difference in the presence of uncontrolled asthma between the two groups became most evident from mid-gestation onwards (Figure 1). In contrast to asthma control, the likelihood (unadjusted RR 0.73; adjusted RR 0.70; 95%CI 0.35-1.41) and incidence (unadjusted IRR 0.70; adjusted IRR 0.66; 0.35-1.26) of exacerbations across the two groups was similar (Table 3).

Discussion

This prospective cohort study provides evidence that the presence of a history of maternal depression/anxiety is associated with a greater prevalence and incidence of uncontrolled asthma during pregnancy. There was no observed increased risk or rate of asthma exacerbations regardless of the presence or absence of depression/anxiety. The outcomes of uncontrolled

asthma and asthma exacerbations were analysed separately as both have been observed to be more common during pregnancy^{23,24}.

This study has built on previous work by examining asthma control in a population with of women with a history of depression/anxiety. Quality of life, anxiety, perceived control of asthma and perceived risks of asthma medications were examined previously in pregnant, asthmatic women²⁵. Overall the pregnant, asthmatic women reported a good quality of life, perceived they had control of their asthma and had low levels of anxiety²⁵. However, the more a pregnant woman was affected emotionally by her asthma, the more frequently she experienced uncontrolled asthma²⁵. Women overestimated the risk of harm to the foetus of asthma medications, though this did not appear to lead to greater anxiety²⁵. Asthma-specific quality of life has also been used previously to examine asthma exacerbations during pregnancy²⁶. An association was observed between an increase in asthma-specific quality of life in early pregnancy and a decrease in the risk of a subsequent asthma exacerbation²⁶. The current study differs from previous work in pregnant women, by comparing asthma control during pregnancy in women with a history of depression or anxiety to women without these complications, rather than the woman's emotional response or perceived quality of life. While this work supports a link between mental health status and uncontrolled asthma during pregnancy, we could not confirm a link between mental health status and asthma exacerbations during pregnancy.

Our study in pregnant asthmatics follows on from previous work in non-pregnant asthmatics demonstrating associations between depression and anxiety and asthma control. Non-pregnant asthmatics with uncontrolled asthma are more likely to suffer from depression than those who are controlled⁹. As depression severity increases, asthma control declines⁹. Respiratory

symptoms were increased in non-pregnant asthmatics with anxiety and depression compared to those without, with Hospital Anxiety Depression Scale (HADS) score being the most useful determinant of night-time symptoms and attacks of breathlessness⁸. This work contributes to the current understanding of mental health status and asthma control by broadening the research to include pregnant women. The fact that the association between depression/ anxiety and poor asthma control still holds in pregnancy suggests that a woman's mental health history can have an overreaching effect on her health during pregnancy through interactions with other complications such as asthma. This will have implications for the provision of appropriate antenatal care to these women at higher risk of uncontrolled asthma.

The observed association between mental illness and poor asthma control could relate to a variety of factors and include the presence of the mental illness itself and a potential direct effect it has on asthma control potentially through alterations in underlying immunological function, or the presence of other co-morbidities or factors often associated with mental illness (e.g. social issues, obesity, smoking).

While relatively little is known about the impacts of depression or anxiety on immunological function in asthmatics, recent studies using pregnant animals report significant neuro-immune alterations of an anti-inflammatory phenotype in the brain that may drive postnatal depression²⁷. Given asthma is driven by an anti-inflammatory immune phenotype the effects of this systemic milieu on the brain may increase the risk of depressive disorders. While a direct effect of asthma is biologically plausible, there is a moderate amount of evidence linking key factors that are often associated with mental illness, such as obesity²⁸, smoking²⁹, poor diet³⁰, impaired health literacy, low socioeconomic status^{20, 21} and poor asthma control.

We attempted to account for these factors as much as possible and for those that we measured (obesity, smoking status, socioeconomic status), they were not statistically significantly different between the two groups. One potential explanation for this lack of difference between the two groups was that our study recruited from a socially disadvantaged population. Both women with and without a history of depression/anxiety predominantly lived in a disadvantaged area and were consequently more exposed to social stressors during their pregnancies such as insecure housing, financial difficulties, relationship breakdown, domestic violence and unemployment¹². While this makes it unlikely that the observed differences in the group of women with depression or anxiety are due to these associated co-morbidities and related social issues, the potential for residual confounding effects remain.

Other potential explanations for the differences in asthma control between the two groups could relate to differences in medication adherence and asthma self-management skills. Non-adherence to asthma medications during pregnancy could be due to limited health literacy in relation to asthma self-management because women do not understand when to use medications or what a loss of asthma control actually entails, or due to fears of medications harming their baby. While not specifically investigated in this study, previous work has demonstrated that women overestimate the risk that asthma medications pose to their unborn child²⁵.

This study was limited by the way in which depression and anxiety were defined. There was no doctor diagnosis, instead it was self-reported with participants who answered yes to the question “Have you ever had depression or anxiety?” being considered to have depression/anxiety. As there is still stigma associated with mental health issues there is the slight possibility that some women did not disclose depression/anxiety and have been misidentified. However, as this

question was asked by a nurse in the clinical setting of the patient's first antenatal visit we have confidence that women did disclose appropriately. The EPDS and the ANRQ, while not being diagnostic tools, did give a good indication of the depression and anxiety risk profiles of the women, regardless of their self-report answer. EPDS and ANRQ scores were also correlated in those women who reported having a history of depression/anxiety. Previous studies have validated these questionnaires as appropriate tools for identifying depression in an antenatal setting and within an Australian population which strengthens the confidence in this data^{19, 20}. Of the women with a history of depression/anxiety, 18.8% had a high EPDS and 78.5% had a high ANRQ compared to 4.3% and 17.2% respectively, of the women without depression/anxiety.

A further limitation of the study was the way in which the outcomes were defined. An asthma exacerbation was self-reported and consisted of an unscheduled doctor's visit, a course of oral corticosteroids, an emergency department presentation or a hospital admission. By its very nature, for an exacerbation to occur and be reported as such, the patient needed to take some action. This can be subject to bias if for some reason the patient does not take the appropriate action for example through a lack of understanding of asthma control (i.e. poor health literacy), lack of money to pay for medications or a lack of access to a doctor which is common within a socially disadvantaged community. Therefore, the actual number of exacerbations may be under-reported and this would affect the results, such that a woman who is not considered to have exacerbated during pregnancy may have actually had an exacerbation. However, these measurements for an exacerbation are internationally recognised and considered appropriate. Both uncontrolled asthma and exacerbations have been observed to be more common during pregnancy^{23, 24}. Appropriate asthma control throughout pregnancy and not just the avoidance of

exacerbations could be important for maternal and foetal health. Future work should assess other maternal and foetal outcomes (such as pre-eclampsia, preterm birth and small for gestational age babies) to examine whether there are any associations with the increase in uncontrolled asthma with a history of depression/anxiety and adverse pregnancy outcomes.

A further limitation of this study relates to the potential generalisability of study findings. The women recruited for this study were in a region of high social disadvantage and as this is the first study to explore the relationship between maternal depression/anxiety and asthma control during pregnancy in a longitudinal fashion, it is unclear whether the findings are generalizable to all pregnant women with co-morbid asthma and depression/anxiety.

In conclusion, a history of maternal depression or anxiety is associated with a significantly increased risk of asthmatic women experiencing poor asthma control during pregnancy. Our findings overall are consistent with those from studies undertaken in non-pregnant adults and highlights the need to manage asthma during pregnancy in a holistic manner that incorporates assessment, evaluation, and management of various co-morbidities. Depression and anxiety may be a significant contributor to a reduced ability for pregnant women to appropriately manage their asthma and seek assistance to do so. It is obvious that a multidisciplinary approach is required for the management of asthma during pregnancy including care associated with mental health management.

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Table 1. Maternal characteristics according to self-reported history of depression and anxiety during pregnancy

	Without Depression/Anxiety (n=104)	With Depression/Anxiety (n=85)	p-value
Age, median (IQR)	25 (22 – 29)	25 (22 – 30)	0.821
BMI, median (IQR)	28 (23 – 33)	27 (23 – 32)	0.938
Parity, n (%):			0.537
0	45 (43.3)	33 (38.8)	
≥1	59 (56.7)	52 (61.2)	
Ethnicity, n (%):			0.094
Caucasian	93 (89.4)	83 (97.6)	
Other	11 (10.6)	2 (2.4)	
Smoking Status, n (%)			0.084
Non-smoker	58 (55.8)	34 (40.0)	
Former smoker	18 (17.3)	18 (21.2)	
Quit during pregnancy	8 (7.7)	15 (17.6)	
Current smoker	20 (19.2)	18 (21.2)	
FEV1 L, mean (SD)	2.92 (0.38)	3.18 (0.46)	0.004
FEV1 % Predicted, mean (SD)	91% (10)	94% (13)	0.210

FVC L, mean (SD)	3.55 (0.46)	3.94 (0.62)	0.001
FEV/FVC % Predicted, mean (SD)	82 (6)	81 (5)	0.307
ICS use before pregnancy, n (%)			0.172
None	72 (69.2)	56 (65.9)	
ICS	9 (8.7)	4 (4.7)	
ICS + LABA	23 (22.1)	25 (29.4)	
Total ANRQ, median (IQR)	11 (7 – 18)	29 (23 – 39)	<0.001
High ANRQ, n (%)	27 (26.7)	70 (87.5)	<0.001
Total EPDS, median (IQR)	4 (2 – 6)	7 (3 – 10)	<0.001
High EPDS, n (%)	4 (4.3)	15 (18.8)	0.002
STAI-6, median (IQR)	30 (20-40)	37 (20-43)	0.219
Antidepressant use, n (%)	0 (0)	18 (21.2)	<0.001

Abbreviations: IQR, interquartile range; BMI, body mass index; FEV, forced expiratory volume; SD, standard deviation; ICS, inhaled corticosteroid; LABA, long acting beta agonist; ANRQ, antenatal risk questionnaire; EPDS, Edinburgh Postnatal Depression Scale; STAI, state trait anxiety inventory

Table 2. Asthma related outcomes during pregnancy according to self-reported presence of depression and anxiety

	Without Depression/Anxiety (n=104)	With Depression/Anxiety (n=85)	p-value
Number of Antenatal Asthma Study Visits Attended, median (range)	4 (3-4)	3 (3-4)	0.095
Moderate/Severe Exacerbation, n (%)	24 (23.1) ^a	17 (20.0) ^a	0.610
Uncontrolled Asthma, n (%)	34 (32.7) ^a	45 (52.9) ^b	0.005
No. of Uncontrolled Asthma Events, median (IQR)	0 (0- 1)	1 (0- 2)	0.005
No. of Asthma Exacerbations, median (IQR)	0 (0- 0)	0 (0- 0)	0.377
Recurrent Uncontrolled Asthma (ACQ6>1.5 on ≥2 study visit), n (%)	10 (9.6%)	20 (23.5%)	0.009
Exacerbations			
GP visit, n (%)	19 (18.3)	12 (14.1)	0.443
OCS use, n (%)	7 (6.7)	7 (8.2)	0.694
ED presentation, n (%)	7 (6.7)	3 (3.5)	0.328

Hospital Admission, n (%)	1 (1.0)	1 (1.2)	0.886
ICS prescribed during pregnancy, n (%)			0.839
None	56 (53.8)	46 (54.1)	
ICS	8 (7.7)	4 (4.7)	
ICS + LABA	8 (7.7)	6 (7.1)	
Already on ICS	32 (30.8)	29 (34.1)	

Abbreviations: IQR, inter quartile range; GP, general practitioner; OCS, oral corticosteroid; ED, emergency department; ICS, inhaled corticosteroid; LABA, long acting beta agonist

Table 3. Relative risk of asthma exacerbations, uncontrolled asthma, and recurrent uncontrolled asthma according to maternal self-reported depression and anxiety during pregnancy

Outcome	HR	95% CI	aHR[†]	95% CI
Moderate/Severe Exacerbation	0.73	0.36-1.47	0.70	0.35-1.41
Uncontrolled Asthma	1.82	1.10-3.01	1.67	1.03-2.72
	RR	95% CI	aRR	95% CI
Recurrent Uncontrolled Asthma (ACQ6>1.5 on ≥ 2 study visit)	2.75	1.24-6.08	1.98	1.00-3.91
	IRR	95% CI	aIRR	95% CI
Number of Moderate/Severe Exacerbations	0.70	0.35-1.38	0.66	0.35-1.26
Number of Mild Exacerbations	1.90	1.21-2.97	1.71	1.13-2.58

Abbreviations: HR, hazard ratio; RR, relative risk; ACQ, asthma control questionnaire; IRR, incidence rate ratio

[†]Adjusted for maternal age, smoking status, parity, BMI, and baseline ICS use

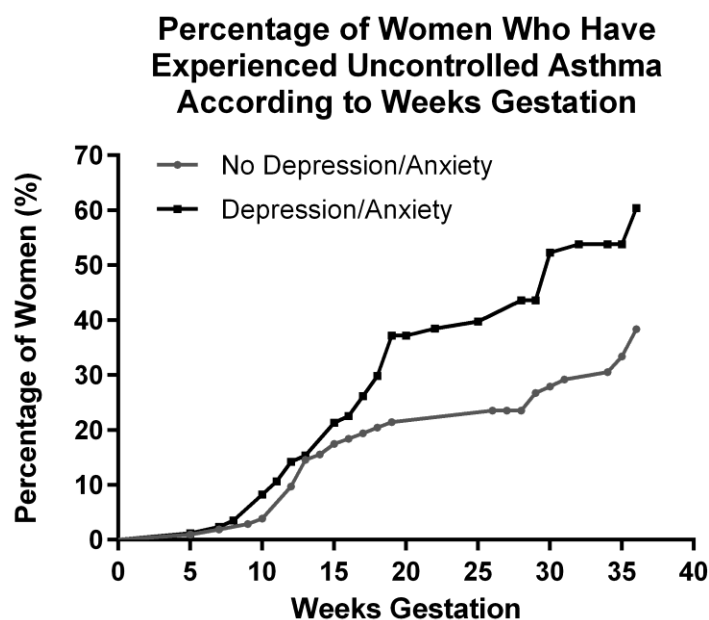


Figure 1: Percentage of women who have experienced uncontrolled asthma according to weeks gestation. The percentage of pregnant women with asthma either with (n=104) or without (n=85) a diagnosis of depression or anxiety were identified as having uncontrolled asthma at each study visit if they had a mean asthma control questionnaire score of greater than 1.5 at the time of the study visit. The cumulative percentage of uncontrolled events identified over gestation has been reported in the current figure.

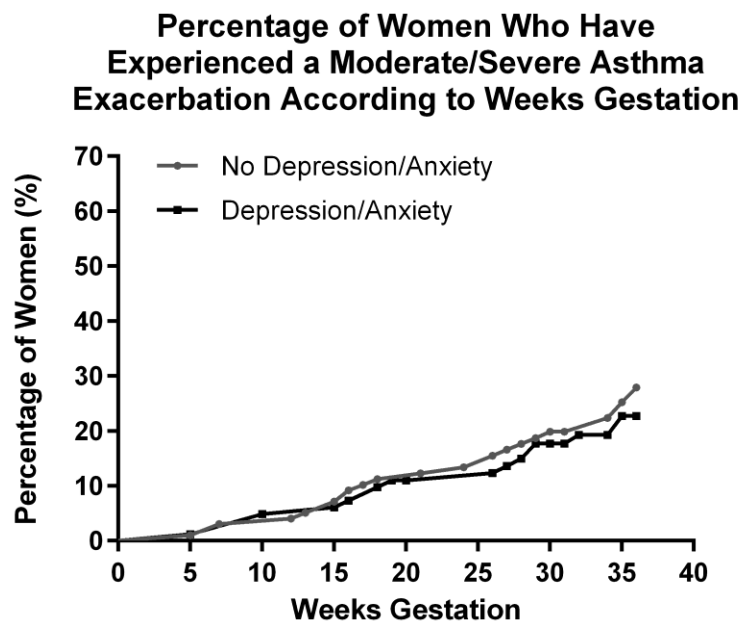


Figure 2: Percentage of women who have experienced a moderate/severe asthma exacerbation according weeks of gestation. Pregnant women with asthma either with (n=104) or without (n=85) a diagnosis of depression or anxiety were identified as having uncontrolled asthma at each study visit if they had a mean asthma control questionnaire score of greater than 1.5 at the time of the study visit. The cumulative percentage of women experiencing a moderate/severe exacerbation over gestation has been reported in the current figure