



A Prospective Study of Respiratory Viral Infection in Pregnant Women With and Without Asthma

Vanessa E. Murphy, PhD; Heather Powell, MMedSc(ClinEpid); Peter A. B. Wark, BMed, PhD; and Peter G. Gibson, MBBS

Background: Respiratory viral infections are common in pregnancy, but their health impact, especially in asthma, is unknown. The objective of this study was to assess the frequency, severity, and consequences of respiratory viral infection during pregnancy in women with and without asthma.

Methods: In this prospective cohort study, common cold symptoms were assessed during pregnancy in 168 women with asthma and 117 women without asthma using the common cold questionnaire and by self-report. Nasal and throat swabs were collected for suspected infections and tested by polymerase chain reaction for respiratory viruses. Pregnancy and asthma outcomes were recorded.

Results: Pregnant women with asthma had more prospective self-reported and questionnaire-detected common colds than pregnant women without asthma (incidence rate ratio, 1.77; 95% CI, 1.30-2.42; $P < .0001$). Retrospectively reported common colds in early pregnancy and post partum were increased in women with asthma compared with women without asthma. The severity of cold symptoms was also increased in women with asthma (total cold score median, 8; interquartile range [5, 10] in women with asthma vs 6 [5, 8] in control subjects; $P = .031$). Among women with asthma, having a laboratory-confirmed viral infection was associated with poorer maternal health, with 60% of infections associated with uncontrolled asthma and a higher likelihood of preeclampsia.

Conclusions: Pregnant women with asthma have more common colds during pregnancy than pregnant women without asthma. Colds during pregnancy were associated with adverse maternal and pregnancy outcomes. Prevention of viral infection in pregnancy may improve the health of mothers with asthma.

CHEST 2013; 144(2):420-427

Abbreviations: ACQ = Asthma Control Questionnaire; CCQ = common cold questionnaire; IQR = interquartile range; IRR = incidence rate ratio; MAP = Managing Asthma in Pregnancy; PCR = polymerase chain reaction; RR = relative risk

Pregnant women, especially those with asthma, experience significant problems associated with respiratory viral infections.¹ The outcomes from pandemic 2009 influenza A(H1N1) were more severe in preg-

nant women and people with asthma,² and retrospective studies report more infections in pregnant women with asthma than those without asthma.^{3,4} The effects of viral infection may be more severe among pregnant women with asthma, with a 10-fold increased risk of respiratory-related hospitalization during the influenza season described for pregnant women with

Manuscript received August 6, 2012; revision accepted February 19, 2013.

Affiliations: From the Centre for Asthma and Respiratory Diseases (Drs Murphy, Wark, and Gibson and Ms Powell), University of Newcastle and Hunter Medical Research Institute; and John Hunter Hospital (Ms Powell and Drs Wark and Gibson), Newcastle, NSW, Australia.

Funding/Support: This study was funded by the University of Newcastle, Asthma Foundation of NSW, and the National Health and Medical Research Council of Australia (NHMRC) [Grant 455593]. Dr Murphy was the recipient of an NHMRC Australian Research Training Fellowship (part-time). Dr Gibson is an NHMRC Practitioner Fellow.

Correspondence to: Vanessa E. Murphy, PhD, Centre for Asthma and Respiratory Diseases, Level 2, W Wing, Hunter Medical Research Institute, c/- University of Newcastle, University Dr, Callaghan, NSW 2308, Australia; e-mail: vanessa.murphy@newcastle.edu.au

© 2013 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.12-1956

asthma compared with women without asthma.¹ Respiratory viral infections are reported to be a significant cause of asthma exacerbations during pregnancy⁵ and may be associated with adverse outcomes, such as low birth weight.⁶

The characteristics and mechanisms of these effects are not well understood. Among nonpregnant women with asthma, susceptibility to respiratory viral infection is not increased, but colds are more severe with more lower respiratory tract symptoms, which are longer lasting.⁷ However, pregnant women may be more susceptible to viral infection because of a pregnancy-related impairment in antiviral interferon responses^{8,9} or deficiencies in epithelial cell function, overproduction of mucus, or alveolar macrophage dysfunction.¹⁰

We hypothesized that during pregnancy, women with asthma experience more frequent and more severe respiratory viral infections than pregnant women without asthma. We assessed these effects prospectively during pregnancy by assessing common colds by self-report and using the common cold questionnaire (CCQ) and polymerase chain reaction (PCR) testing and retrospectively in early pregnancy and post partum.

MATERIALS AND METHODS

Study Design

Pregnant women with and without asthma were recruited from April 2007 to November 2009 (Fig 1) at the antenatal clinic of John Hunter Hospital, Newcastle, Australia. Written informed consent was obtained and ethics approval granted by the University of Newcastle and Hunter New England Area Health Service Research Ethics Committees (approval number 07/02/21/3.06). Women between 12 and 20 weeks' gestation who were > 18 years of age were included. Exclusion criteria were the presence of a chronic medical disease (other than asthma), drug or alcohol dependence, and an inability to attend study visits or perform spirometry. Control subjects had never received a diagnosis of asthma, whereas women with asthma had a doctor's diagnosis of asthma and asthma symptoms or therapy in the prior 3 months.

Women completed monthly clinical visits and were telephoned fortnightly (e-Appendix 1, e-Fig 1). The majority (157 of 168, 93%) of the women with asthma also commenced participation in the Managing Asthma in Pregnancy (MAP) study.^{11,12} Regardless of coparticipation in MAP, all women, with and without asthma, had the same schedule of study visits and telephone contacts and were eligible for additional visits based on the same criteria (current common cold). Some women consented to donate blood for in vitro studies of responses to viral infection.^{8,9}

Clinical Measures

At each visit and telephone contact, asthma symptoms over the past 7 days were collected by self-report and using the Asthma Control Questionnaire (ACQ7).¹³ Exacerbations were assessed by direct questioning and defined as those requiring medical intervention (hospital admission, ED presentation, unscheduled doctor visit, or the use of oral corticosteroids).

Common colds were assessed by direct questioning (self-report: "Do you currently have a cold?") and using the CCQ (e-Fig 2)¹⁴ at

each contact. The CCQ assessed nine symptoms over four domains (general: fevers, chills, muscle pains; nasal: watery eyes, runny nose, sneezing; throat: sore throat; chest: cough, chest pain), which were scored as none (0), mild (1), moderate (2), or severe (3).¹⁴ A cold was "probable" when symptoms were moderate in at least two domains or mild in at least three domains. Unless otherwise indicated, a common cold was defined as instances wherein the CCQ indicated a "probable cold." Common cold severity was assessed by the total CCQ score (possible score, 0-27) and by the proportion of colds with a score ≥ 10 .¹⁴ Baseline scores are given in e-Table 1. Colds in early pregnancy and post partum were retrospectively assessed by self-report at the first study visit and 6 months post partum, respectively. Subjects with a current cold (women with and without asthma) or current asthma exacerbation were offered additional visits either at home or hospital within 48 h. If a new cold was reported 14 days after a previous report, it was considered a separate clinical event.⁷

Virus PCR Testing

Nasal and throat swabs were collected from women with common colds. Viruses were identified using real-time quantitative PCR for rhinovirus, enterovirus, respiratory syncytial virus A and B, influenza A and B, coronavirus, and human metapneumovirus.¹⁵

Statistical Methods

Statistical analysis was performed using Stata 11 (StataCorp LP). Results are presented as mean $\pm$ SD or median (interquartile range [IQR]) with Student *t* test and Wilcoxon rank sum tests as appropriate and Wilcoxon signed rank test for paired data. The χ^2 test was used to compare proportions. Two-sided tests with $P < .05$ were considered significant, with the exception of data on the frequency of common colds and PCR-positive colds ($P < .025$, because this outcome was assessed by two similar methods). The rate difference between the groups for colds was compared using a Poisson regression model adjusted for BMI, atopy, and parity, with a robust option when data were overdispersed. Secondary outcomes were cold severity (analyzed as panel data using Stata's xtreg with random effects and adjusted for baseline CCQ score, BMI, atopy, and parity), impact of colds on asthma, and impact of colds on pregnancy outcomes. We assessed the relationship between PCR-positive colds in asthma and preeclampsia/pregnancy-induced hypertension with logistic regression, adjusting for smoking, parity, age, BMI, and multiple pregnancy. Receiver operator curve (ROC) analyses were used to evaluate different diagnostic cut-off levels for the CCQ score in PCR positive infections (e-Fig 3). Kaplan-Meier survival estimates were used to investigate the time to first cold (e-Fig 4).

RESULTS

Subject Characteristics

Two hundred eighty-five pregnant women were recruited (168 with asthma, 117 control subjects) (Fig 1). Pregnant women with asthma had significantly higher BMI ($P < .002$), significantly worse lung function ($P < .05$), and were more likely to have atopy ($P < .0001$) than control subjects (Table 1, e-Appendix 2, e-Table 2).

Frequency of Common Colds During Pregnancy

Pregnant women with asthma had more questionnaire-detected common colds during pregnancy (71%) than pregnant women without asthma (46%; $P < .0001$;

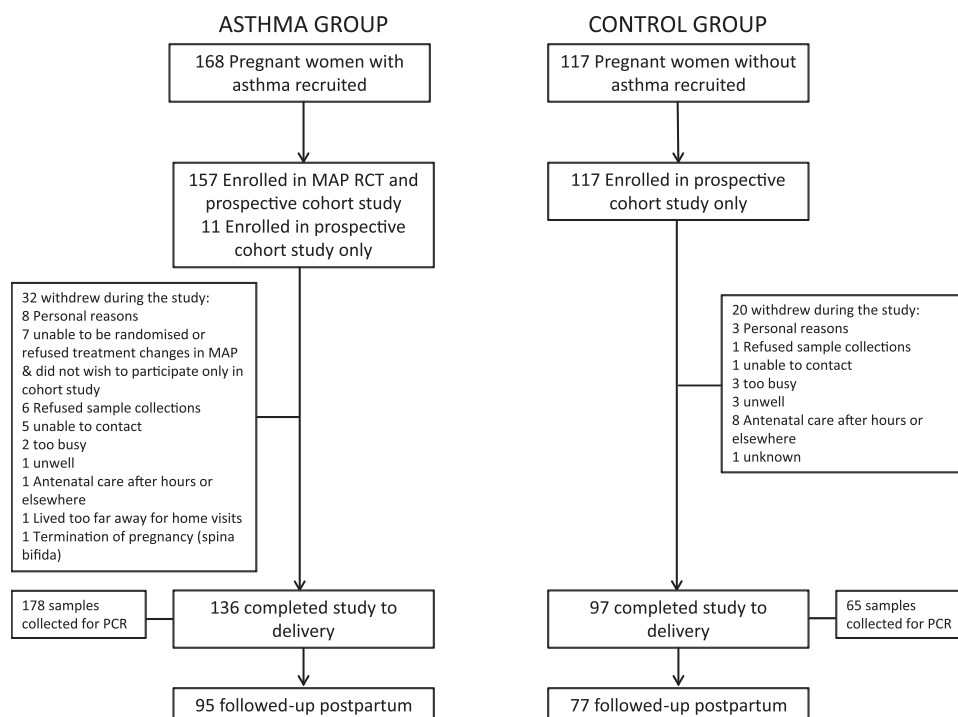


FIGURE 1. Recruitment, enrollment, and study completion. MAP = Managing Asthma in Pregnancy; RCT = randomized controlled trial.

relative risk [RR], 1.83; 95% CI [1.39, 2.41]) (Table 2). More women with asthma had multiple common colds than women without asthma (33% vs 16%; $P = .0028$; RR, 1.25; 95% CI [1.09, 1.42]). There were 223 common cold events in the asthma group and 83 in the control group (e-Table 3). The rate of common cold events adjusted for follow-up time, atopy, parity, and maternal BMI was significantly higher in the asthma group compared with the control group (Fig 2) (incidence rate ratio [IRR], 1.77; 95% CI [1.30, 2.42]; $P < .0001$). The control group had the same proportion of common colds detected in the second and third trimesters, whereas the asthma group had significantly more common colds detected in the second compared with the third trimester (Table 2) ($P < .0001$), despite longer follow-up times for the third trimester. In addition to questionnaire-detected colds, women with asthma also self-reported more colds prospectively during pregnancy and retrospectively in early pregnancy and post partum (e-Table 4).

Nasal and/or throat swab samples were collected from 80% of common cold events (20% were not collected because of refusal by the participant or lack of a clinical visit at the time of the event), within a median time from symptom onset of 3.5 days (IQR, 3-7 days) in the control group and 4 days (IQR, 2-7 days) in the asthma group (e-Table 5). Thirty-one percent of women with asthma and 18.8% of women without asthma had one or more PCR-

positive colds during pregnancy (RR, 1.18; 95% CI [1.03, 1.34], asthma vs control) (Fig 3, Table 3), but this did not reach our significance level of $P < .025$ ($P = .0305$). There were 26 PCR-positive cold events in the nonasthmatic control group and 60 PCR-positive cold events in the asthma group (e-Table 5). There was no significant difference in the rate of PCR-positive colds between groups (adjusted for follow-up time, atopy, parity, and maternal BMI; IRR, 1.18; 95% CI [0.72, 1.94]; $P = .505$) (Table 3). The number of second trimester PCR-positive colds was higher than the number of third trimester colds in the asthma group ($P = .0442$) but not in the control group ($P = .4524$) (e-Table 5). In addition to questionnaire-detected colds, women with asthma also self-reported more colds prospectively during pregnancy and retrospectively in early pregnancy and post partum (e-Table 4).

Severity of Common Colds During Pregnancy

The median total CCQ score was higher among common cold events in the asthma group (median, 8; IQR [5, 10]) compared with the control group (median, 6; IQR [5, 8]) and was statistically significant when baseline values were adjusted for (xtreg, coefficient 1.16; 95% CI [0.11, 2.21]; $P = .031$) (e-Table 6). However, in PCR-positive colds, the total CCQ score was not different between groups (e-Table 6) (xtreg, coefficient 0.86; 95% CI [-1.13, 2.85]; $P = .397$).

Table 1—Subject Characteristics

Characteristic	Control Group (n = 117)	Asthma Group (n = 168)	P Value
Maternal age, ^a y	29.6 (4.6) Range, 18-38	28.5 (5.6) Range, 18-43	.086
Gestational age at recruitment, ^a wk	16.6 (2.3) Range, 12.6-21.3	16.9 (2.4) Range, 11.7-21.9	.193
Gravidity ^b	2 (1, 2)	2 (1, 3)	.010
Parity ^b	1 (0, 1)	1 (0, 2)	.016
Para 0 ^c	49 (41.9)	56 (33.3)	.178
Maternal atopy ^c	51 (45.9) n = 111	115 (71.9) n = 160	< .0001
Maternal BMI ^b	25.2 (22.8, 28.7) n = 116	27.7 (24.4, 32.1) n = 165	.0005
Smoking status			...
Never ^c	66 (56.4)	80 (47.6)	...
Ex ^c	32 (27.4)	52 (31.0)	...
Current ^c	18 (15.4)	35 (20.8)	.245
Smoking pack-y ^b	3.0 (0.9, 6.0) n = 117	4.0 (1.5, 7.0) n = 142	.070
Prebronchodilator spirometry			...
FEV ₁ ^a	3.29 (0.42)	2.96 (0.52)	< .0001
% Predicted FEV ₁ ^a	102.9 (11.1)	93.8 (14.6)	< .0001
FVC ^b	3.93 (3.52, 4.24)	3.72 (3.34, 4.18)	.030
% Predicted FVC ^b	107.6 (98.0, 116.2) n = 116	103.0 (74.5, 112.6)	.037
No ICS treatment ^d	...	120 (71.4)	...
ICS treatment ^d	...	15 (8.9)	...
ICS/LABA treatment ^d	...	33 (19.6)	...
ICS dose (among ICS users), BDP equivalents µg/d	...	800 (650, 1,000) n = 47	...
ACQ7	...	0.86 (0.29, 1.57)	...
Influenza vaccine for current season ^c	10 (8.5)	16 (9.5)	.8407

Data were collected at the first study visit. ACQ7 = Asthma Control Questionnaire (7 item); BDP = beclomethasone dipropionate; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β-agonist.

^aMean (SD), Student *t* test.

^bMedian (IQR), Wilcoxon rank sum test.

^cNo. (%), χ² test.

^dNo. (%).

Impact of Colds on Asthma

One-third of the PCR-positive viral infections were associated with exacerbation requiring medical intervention and a further one-third with loss of control (e-Tables 7, 8). Total CCQ score significantly correlated with ACQ score (Spearman *r* = 0.3187, *P* = .0131, Spearman rank correlation) (e-Fig 5).

Among the subgroup of women with asthma participating in the MAP study, those randomized to fractional exhaled nitric oxide-based management (n = 69) were significantly less likely to report common colds (63.8% vs 82.2%; RR, 0.492; 95% CI [0.274, 0.881]) or PCR-positive colds (23.2% vs 42.5%; RR, 0.749; 95% CI [0.592, 0.948]) compared with those randomized to clinical guidelines-based management (n = 73).

Impact of Colds on Neonatal Outcomes

In the control group, women with at least one PCR-positive cold had babies of significantly lower birth weight (*P* = .0274) and length (*P* = .0236) compared with control subjects with PCR-negative colds

(Table 4). Women with asthma with PCR-positive colds had significantly increased odds of preeclampsia or pregnancy-induced hypertension when adjusted for known preeclampsia risk factors (maternal smoking, age, BMI, parity, multiple pregnancy; OR, 8.48; 95% CI [1.41, 51.11]; *P* < .02) (Table 4) compared with women with asthma with PCR-negative colds.

DISCUSSION

Pregnant women with asthma have more common colds during pregnancy than pregnant women without asthma, both by self-report and questionnaire. The severity of symptoms was higher in subjects with asthma with common colds than control subjects, when adjusted for baseline differences. Although PCR-positive colds were of similar severity in the two groups, virus-confirmed colds in subjects with asthma frequently resulted in exacerbations and were associated with perinatal effects.

Previous studies in nonpregnant adults with asthma have suggested that subjects with asthma are no more

Table 2—Frequency of Common Colds During Pregnancy

Cold Measures	Control (n = 117)	Asthma (n = 168)	Effect Size	P Value
Subjects with ≥ 1 cold (probable by CCQ) during pregnancy ^a	54 (46)	120 (71.4)	RR, 1.83; 95% CI (1.39, 2.41)	< .0001
Subjects with > 1 common cold during pregnancy ^a	19 (16.2)	55 (32.7)	RR, 1.25; 95% CI (1.09, 1.42)	.0028
No. of colds per person ^b	0 (0, 1)	1 (0, 2)	...	< .0001
	Range, 0-6	Range, 0-8		
No. of common cold events/person-wk ^c	0.035	0.067	IRR, 1.77; 95% CI (1.30, 2.42)	< .0001
Cold events by season			...	...
Summer ^d	13 (15.7)	33 (14.8)		
Autumn ^d	24 (28.9)	53 (23.8)		
Winter ^d	26 (31.3)	75 (33.6)		
Spring ^d	20 (24.1)	62 (27.8)		

Seasons were Australian summer (December-February), autumn (March-May), winter (June-August), spring (September-November). CCQ = common cold questionnaire; IRR = incidence rate ratio; RR = relative risk. See Table 1 legend for expansion of other abbreviation.

^aNo. (%), χ^2 test, RR.

^bMedian (IQR), Mann-Whitney test.

^cIRR, Poisson regression, adjusted for atopy, parity, and BMI.

^dNo. (%).

susceptible to respiratory tract infections than subjects without asthma.⁷ The evidence in the present study suggests that in pregnancy, women with asthma may be more susceptible to common colds than women without asthma but that cold symptoms associated with PCR-positive colds are similar to those in women without asthma. In a large prospective study, 14.4% of women had a common cold during pregnancy, with one-half of these colds medically recorded.¹⁶ The CCQ we used identified more common colds than self-report, and not all of these were virus-positive by laboratory testing. The prospective nature of our study likely contributed to a high rate of reporting of common colds. It is possible that confounding by symptoms of rhinitis may have contributed to a high proportion of women with questionnaire-detected colds.

Common colds were more likely to occur in the second trimester than the third trimester in the asthma group only. Bánhidý et al¹⁶ found that there was a lower prevalence of the common cold in the eighth and ninth months of pregnancy compared with the first

7 months; however, it was unclear if follow-up time and early deliveries had been accounted for. Asthma exacerbations also peak in the late second trimester.^{5,17} Further evidence is required to determine if this is due to a pregnancy-specific rise in susceptibility to infection.

One-third of PCR-positive colds were associated with exacerbations requiring medical intervention. In previous studies, 60% of cases with a positive virus identification were associated with asthma exacerbation,¹⁸ whereas cold severity was predictive of subsequent asthma worsening.¹⁹ Viral infection is a significant asthma trigger, possibly because of the inflammatory pathways activated during infection. Understanding the relationship between viral infection and asthma²⁰ is important, as preventing viral infection could also prevent exacerbations. We have evidence that improved asthma management through fractional exhaled nitric oxide monitoring is associated with a reduction not only in exacerbations¹¹ but also in PCR-positive viral infections.

Pregnant women with asthma who had PCR-positive colds were more likely to have preeclampsia than

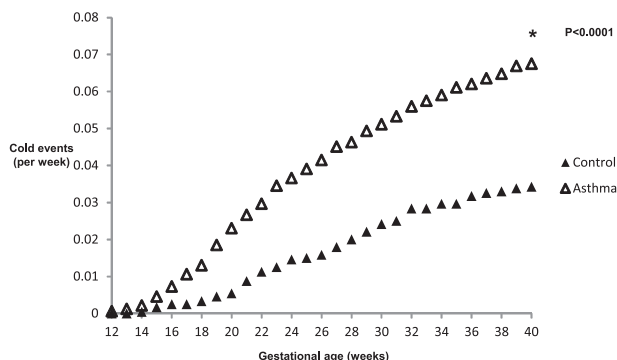


FIGURE 2. Cumulative common colds adjusted for total person-weeks per group in the asthma (Δ) and control (▲) groups over the course of pregnancy (*incidence rate ratio, 1.77; 95% CI [1.30, 2.42]).

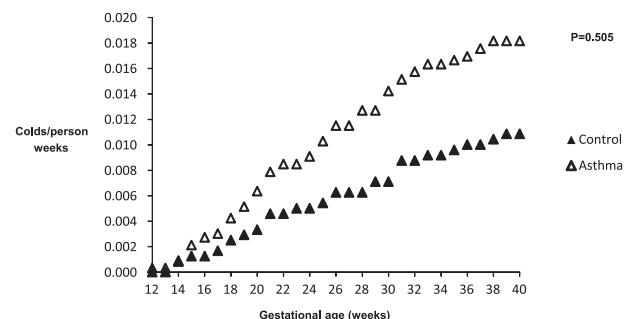


FIGURE 3. Cumulative polymerase chain reaction-positive colds adjusted for total person-weeks per group in the asthma (Δ) and control (▲) groups over the course of pregnancy (incidence rate ratio, 1.18; 95% CI [0.72, 1.94]).

Table 3—Frequency of PCR-Positive Colds During Pregnancy

Cold Measures	Control (n = 117)	Asthma (n = 168)	Effect Size	P Value
Subjects with ≥ 1 PCR-positive cold ^a	22 (18.8)	52 (31.0)	RR, 1.18; 95% CI (1.03, 1.34)	.0305
Subjects with multiple PCR-positive cold events ^a	3 (2.6)	8 (4.8)	...	.5254
PCR colds per person-weeks ^b	0.0108	0.0182	IRR, 1.18; 95% CI (0.72, 1.94)	.505
Influenza A ^c	1 (3.4)	5 (7.7)	...	...
Influenza B ^c	2 (6.9)	3 (4.6)	...	...
Human RV ^c	13 (44.8)	25 (38.5)	...	...
Human EV ^c	1 (3.4)	6 (9.2)	...	...
CoV ^c	3 (10.3)	9 (13.8)	...	...
RSV A ^c	0 (0)	1 (1.5)	...	...
RSV B ^c	4 (13.8)	1 (1.5)	...	...
Human MPV ^c	5 (17.2)	15 (23.1)	...	...
Total viruses detected	29	65	...	...
Multiple infection	RV + MPV	RV + EV	...	...
	RSV B + MPV	RV + CoV	...	...
	RSV B + MPV	CoV + MPV	...	...
	...	RSVA + RV	...	...
	...	FluA + MPV	...	...

CoV = coronavirus; EV = enterovirus; FluA = influenza A; MPV = metapneumovirus; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; RV = rhinovirus. See Table 1 legend for expansion of other abbreviations.

^aNo. (%), χ^2 test, RR.

^bIRR, Poisson regression adjusted for atopy, parity, and BMI.

^cNo. (% of all viruses detected).

women without PCR-positive colds, consistent with studies suggesting an association between maternal infection (bacterial or viral) and the risk of preeclampsia, possibly due to changes in the maternal immune sys-

tem.²¹ Pregnant women with asthma are at increased risk of preeclampsia compared with pregnant women without asthma.²²⁻²⁵ No previous reports have linked asthma, preeclampsia, and viral infection during pregnancy. It

Table 4—Impact of PCR-Positive Colds on Pregnancy Outcomes in the Control Group and the Asthma Group

Pregnancy Outcomes	Control Group			Asthma Group		
	PCR- Colds (n = 24 Pregnancies and Babies)	PCR+ Colds (n = 22 Pregnancies and Babies)	P Value	PCR- Colds (n = 53 Pregnancies, n = 55 Babies)	PCR+ Colds (n = 52 Pregnancies, n = 52 Babies)	P Value
Gestational age, ^a wk	40.8 (39.7, 41.3) n = 22	39.9 (38.7, 41.0) n = 22	.1555	39.9 (38.6, 40.5) n = 54	39.6 (38.4, 40.3) n = 52	.6265
Preterm delivery of infant (< 37 completed wk) ^b	0 of 22	3 of 22 (13.6)	.2316	9 of 54 (16.7)	4 of 52 (7.7)	.2661
Birth weight, ^a g	3,600 (3,384, 3,885) n = 22	3,130 (2,790, 3,673) n = 22	.0274	3,520 (3,180, 3,875) n = 51	3,280 (3,010, 3,520) n = 51	.0605
Low birth weight ($< 2,500$ g) ^b	0 of 22	4 of 22 (18.2)	.1157	5 of 51 (9.8)	4 of 51 (7.8)	.727
Birth length, ^a cm	52 (51.5, 53.5) n = 15	51 (49, 51.9) n = 18	.0236	51 (49, 53) n = 45	50.5 (49, 52) n = 44	.2622
Birth head circumference, ^a cm	34.5 (33.5, 35.5) n = 21	34 (33, 35) n = 20	.0974	34.5 (33.5, 35.4) n = 51	34 (33, 35) n = 51	.3348
Apgar at 1 min ^a	9 (8, 9) n = 21	8 (8, 9) n = 21	.5328	9 (7, 9) n = 50	9 (6, 9) n = 51	.8501
Apgar at 5 min ^a	9 (9, 9) n = 22	9 (9, 9) n = 22	.5561	9 (9, 9) n = 50	9 (9, 9) n = 51	.4819
Maternal preeclampsia ^b	0	1 (4.5)	.3177	0	6 (11.5)	.0355
Maternal pregnancy-induced hypertension ^b	0	1 (4.5)	.3177	2 (3.8)	5 (9.6)	.4338
Maternal gestational diabetes	0	0	...	2 (3.8)	4 (7.7)	.6741
Still birth	0	0	...	1 (1.9)	0	.3241
Neonatal intensive care admission ^b	3 (13.6)	2 (9)	.6348	8 (4.8)	7 (13.5)	.8416
Congenital anomaly ^b	0	1 (4.5)	.3177	0	0	...

Note: Data not available on all infants due to delivery at other hospitals. See Table 1 and 3 legends for expansion of abbreviations.

^aMedian (IQR) Wilcoxon rank sum test.

^bNo. (%), χ^2 test.

is possible that inflammation associated with the response to viral infection and/or asthma exacerbation may contribute to the underlying endothelial dysfunction in preeclampsia.

There are limitations to our study. The CCQ is an unvalidated tool, which limits the conclusions we can make using this instrument, particularly since the CCQ is not validated to distinguish between viral infections and rhinitis. There was the possibility of recall bias for colds assessed retrospectively, although for the majority of pregnancy we collected data prospectively. The pregnant women with asthma had higher parity than pregnant women without asthma, which might increase their exposure to virus infections from other children.^{26,27} However, we adjusted for this as well as other confounders, such as atopy and BMI (a known risk factor for exacerbations in pregnancy²⁸), when considering the rate of colds. Our sample collection time was not ideal, with swabs collected within a median of 3 to 4 days from symptom worsening. We contacted women fortnightly by phone and sent mobile phone text reminders every other week to try to increase participation and offered home visits during colds. The CCQ covers only 2 days of the past 14, and since we did not administer it daily, it is possible colds were missed. The number of PCR-positive colds experienced by women with asthma, when adjusted for follow-up time, was not significantly different from the control group. This may be due to a lack of power, since only a proportion of common colds were tested in the laboratory, or rhinitis-like symptoms and cough may be amplified by asthma or pregnancy themselves, resulting in more colds being detected that were not true infections. Although we found second trimester colds to be more frequent than third trimester colds, it is possible that rhinitis of pregnancy may have contributed to this finding.

CONCLUSIONS

Common colds were more frequently reported among pregnant women with asthma compared with women without asthma. They occurred more often in the second trimester than the third, perhaps explaining the greater exacerbation risk at this time. There was an impact on maternal health, with one-third of infections associated with exacerbations requiring medical intervention. Prevention of respiratory viral infections may improve asthma outcomes during pregnancy.

ACKNOWLEDGMENTS

Author contributions: Dr Murphy takes responsibility for the content of the manuscript, including the data and analysis.

Dr Murphy: contributed to study conception and design, analysis and interpretation of data, and writing the manuscript and gave final approval to the version to be published.

Ms Powell: contributed to analysis and interpretation of data and revision of the article for important intellectual content and gave final approval to the version to be published.

Dr Wark: contributed to acquisition of data and revision of the article for important intellectual content and gave final approval to the version to be published.

Dr Gibson: contributed to study conception and design, interpretation of data, and revision of the article for important intellectual content and gave final approval to the version to be published.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: We thank Kelly Steel, BNursing; Karen McLaughlin, Dip App Sci (Nursing), BNursing, Post Grad Dip Midwifery; Rebecca Oldham, Advanced Dip Pathology testing, B Ed (Sci); Linda Howell, B Nursing; Joanne Smart, Ass Dip DMR; Noreen Bell, RN; and Sandra Dowley for assistance with clinical assessments and data collection; Lakshitha Gunawardhana, B Biotech (Hons); Alan Hsu, PhD; Kristy Parsons, B Biomed Sci; Rebecca Forbes, PhD; and Katherine Baines, PhD, for laboratory testing; and the midwives and staff of the antenatal clinic at John Hunter Hospital for their assistance during subject recruitment.

Additional information: The e-Figures and e-Tables can be found in the "Supplemental Materials" area of the online article.

REFERENCES

1. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol*. 2003;189(6):1705-1712.
2. Jain S, Kamimoto L, Bramley AM, et al. 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1935-1944.
3. Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. *Respiration*. 1998;65(2):130-135.
4. Clifton VL, Engel P, Smith R, Gibson P, Brinsmead M, Giles WB. Maternal and neonatal outcomes of pregnancies complicated by asthma in an Australian population. *Aust N Z J Obstet Gynaecol*. 2009;49(6):619-626.
5. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol*. 2005;106(5 pt 1):1046-1054.
6. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006;61(2):169-176.
7. Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet*. 2002;359(9309):831-834.
8. Forbes RL, Gibson PG, Murphy VE, Wark PA. Impaired type I and III interferon response to rhinovirus infection during pregnancy and asthma. *Thorax*. 2012;67(3):209-214.
9. Forbes RL, Wark PA, Murphy VE, Gibson PG. Pregnant women have attenuated innate interferon responses to 2009 pandemic influenza A virus subtype H1N1. *J Infect Dis*. 2012;206(5):646-653.
10. James KM, Peebles RS Jr, Hartert TV. Response to infections in patients with asthma and atopic disease: an epiphenomenon or reflection of host susceptibility? *J Allergy Clin Immunol*. 2012;130(2):343-351.
11. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of

- exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378(9795):983-990.
12. Powell H, McCaffery K, Murphy VE, et al. Psychosocial outcomes are related to asthma control and quality of life in pregnant women with asthma. *J Asthma*. 2011;48(10):1032-1040.
 13. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.
 14. Powell H, Smart J, Wood LG, et al. Validity of the common cold questionnaire (CCQ) in asthma exacerbations. *PLoS One* 2008;3(3):e1802.
 15. Wark PA, Bucchieri F, Johnston SL, et al. IFN-gamma-induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. *J Allergy Clin Immunol*. 2007;120(3):586-593.
 16. Bánhidó F, Acs N, Puhó E, Czeizel AE. Pregnancy complications and delivery outcomes of pregnant women with common cold. *Cent Eur J Public Health*. 2006;14(1):10-14.
 17. Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax*. 1996;51(4):411-414.
 18. Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infection and exacerbations of asthma in adult patients. *Thorax*. 1988;43(9):679-683.
 19. Walter MJ, Castro M, Kunselman SJ, et al; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. Predicting worsening asthma control following the common cold. *Eur Respir J*. 2008;32(6):1548-1554.
 20. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ*. 1993;307(6910):982-986.
 21. Rustveld LO, Kelsey SF, Sharma R. Association between maternal infections and pre-eclampsia: a systematic review of epidemiological studies. *Matern Child Health J*. 2008;12(2):233-242.
 22. Murphy VE, Namazy JA, Powell H, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011;118(11):1314-1323.
 23. Martel MJ, Rey E, Beaulac MF, et al. Use of short-acting beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol*. 2007;119(3):576-582.
 24. Martel MJ, Rey E, Beaulac MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *BMJ*. 2005;330(7485):230.
 25. Rudra CB, Williams MA, Frederick IO, Luthy DA. Maternal asthma and risk of preeclampsia: a case-control study. *J Reprod Med*. 2006;51(2):94-100.
 26. Johnston SL, Pattemore PK, Sanderson G, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med*. 1996;154(3 pt 1):654-660.
 27. Lain SJ, Roberts CL, Warning J, Vivian-Taylor J, Ford JB. A survey of acute self-reported infections in pregnancy. *BMJ Open*. 2011;1(1):e000083.
 28. Hendler I, Schatz M, Momirova V, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Association of obesity with pulmonary and nonpulmonary complications of pregnancy in asthmatic women. *Obstet Gynecol*. 2006;108(1):77-82.

A Prospective Study of Respiratory Viral Infection in Pregnant Women With and Without Asthma

Vanessa E. Murphy, PhD; Heather Powell, MMedSc(ClinEpid); Peter A. B. Wark, BMed, PhD; and Peter G. Gibson, MBBS

e-Appendix 1.

Methods:

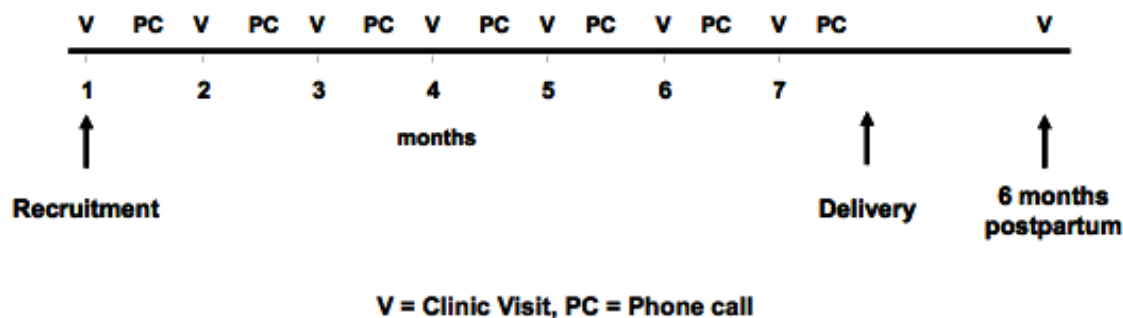
Study design and participants

The majority (157/168, 93%) of the asthmatic women also commenced participation in the Managing Asthma in Pregnancy (MAP) study, which was a randomised controlled trial comparing clinical guideline-based management of asthma using symptoms and lung function, with the management of asthma guided by fractional exhaled nitric oxide (FENO) ¹. The primary results of the RCT in non-smoking women have been previously published, along with a secondary analysis ^{1,2}. 69 of the participants in this study were randomised to the FENO based management intervention of MAP, and 73 subjects to the clinical guidelines-based management intervention of the MAP RCT. 15 subjects commenced MAP but were not randomised. The remaining 11 subjects who did not participate in the RCT were not eligible because they were recruited prior to commencement of the MAP study (n=8), or did not wish to have their medications changed (n=2), or were excluded from the MAP study on the basis of exacerbation history (more than 3 courses of OCS in the past year, n=1)..

Clinical measures

The study visit schedule is depicted in e-Figure 1.

Online supplements are not copyedited prior to posting.



e-Figure 1. Cohort study visit structure for women with asthma and control women without asthma. Additional visits (at the hospital or at home) occurred at any time between recruitment and delivery during common colds or asthma exacerbations.

Lung function (EasyOne Spirometer, NicheMedical, North Sydney, Australia) and FENO (ECOMEDICS, Duernten, Switzerland, at a controlled flow rate of 50 ml/s) were measured at clinical assessments. Maternal height and weight, asthma history and severity were assessed at the first visit, while smoking history, influenza vaccination history, medication use (β_2 -agonists, inhaled (ICS) and oral corticosteroid (OCS) use and asthma self-management skills (device technique, adherence and medications knowledge) were assessed at each clinic visit by direct questioning using previously described methods³. Details on parity, gravidity, marital status, ethnicity and neonatal outcomes were obtained from the subject's medical records.

Atopy was assessed by specific serum IgE against domestic animal mix (contains cat dander, dog dander, guinea pig epithelium, rat and mouse), grass mix (contains Bermuda grass [Cynodon dactylon], Bahia grass, Johnson grass, Kentucky blue grass [meadow grass], rye grass and timothy grass), house dust mix (contains D pteronyssinus, D farinae, house dust and cockroach), mould mix (contains penicillium notatum, Cladosporium herbarium,

Aspergillus fumigatus, *Alternaria alternate*) and weed mix (contains common ragweed, mugwort, plantain, ribwort, goosefoot lamb's quarters, prickly saltwort, russian thistle). Subjects were considered atopic if the specific IgE to aeroallergen was 0.35 kUA/L or greater in venous blood. Exhaled carbon monoxide (ECO) was measured at clinical visits using a piCO Smokerlyzer Breath CO Monitor (Bedfont, UK).

ICS use was expressed as mCS use was expressed as ECO) was measured at clinical visits using a piCO Smokerlyzer Breath CO Monitor (Be1 m S use was expressed as ECO) was measureduticasone dipropionate. Some women used ICS in combination with long acting beta agonist (LABA) either as budesonide/e-formoterol or fluticasone/salmeterol.

Loss of control was defined when women reported 3 or more of the following: daytime symptoms >2 days per week, any activity limitation, any nocturnal symptoms, reliever medication use >2 times per week and peak expiratory flow or FEV₁ <80% predicted.

Women were considered current smokers if they self-reported cigarette smoking, or had an elevated exhaled carbon monoxide ($\text{ECO} \geq 10$ ppm) and/or urinary cotinine ($\geq$ level 5 / 2840 nmol/L, Nicalert, NYMOX, St-Laurent, QC, Canada). ECO was measured at each clinical assessment, while urinary cotinine was measured at the second visit.

Nasal symptoms (blocked nose, runny nose, itchy nose or sneezing), gastric reflux symptoms (indigestion, heartburn, burning feeling), cough and asthma symptoms (breathlessness, cough, wheeze, chest tightness) were also assessed using a visual analogue scale (VAS) 10 cm in length, with subjects asked to mark how bothersome their symptoms were from 0cm (not at all bothersome) to 10cm (extremely bothersome).

The CCQ is not a validated questionnaire. We have calculated the positive predictive value (PPV) and negative predictive value (NPV) of the CCQ for detecting PCR positive respiratory viral infections in pregnancy using 219 data points. The PPV among pregnant women with asthma was 36.8%, and the NPV was 84.4%. Using 86 data points, the PPV among pregnant women without asthma was 40%, while the NPV was 61.3%, giving an overall PPV of 37.6% and NPV of 76.8%. Receiver Operator Curves were constructed (e-Figure 3), but these did not allow a CCQ total score cut-off which was associated with PCR positive infection to be determined. The CCQ has good negative predictive value, and is therefore useful in identifying when infections are unlikely to be present.

COMMON COLD QUESTIONNAIRE				
In the past 2 days, have you experienced any of the following:				
	None	Mild	Moderate	Severe
Category 1: General Symptoms				
Fevers	☐ 0	☐ 1	☐ 2	☐ 3
Chills	☐ 0	☐ 1	☐ 2	☐ 3
Muscle Pains	☐ 0	☐ 1	☐ 2	☐ 3
Category 2: Nasal Symptoms				
Watery Eyes	☐ 0	☐ 1	☐ 2	☐ 3
Runny Nose	☐ 0	☐ 1	☐ 2	☐ 3
Sneezing	☐ 0	☐ 1	☐ 2	☐ 3
Category 3: Throat Symptoms				
Sore Throat	☐ 0	☐ 1	☐ 2	☐ 3
Category 4: Chest Symptoms				
Cough	☐ 0	☐ 1	☐ 2	☐ 3
Chest Pain	☐ 0	☐ 1	☐ 2	☐ 3

e-Figure 2. Common cold questionnaire

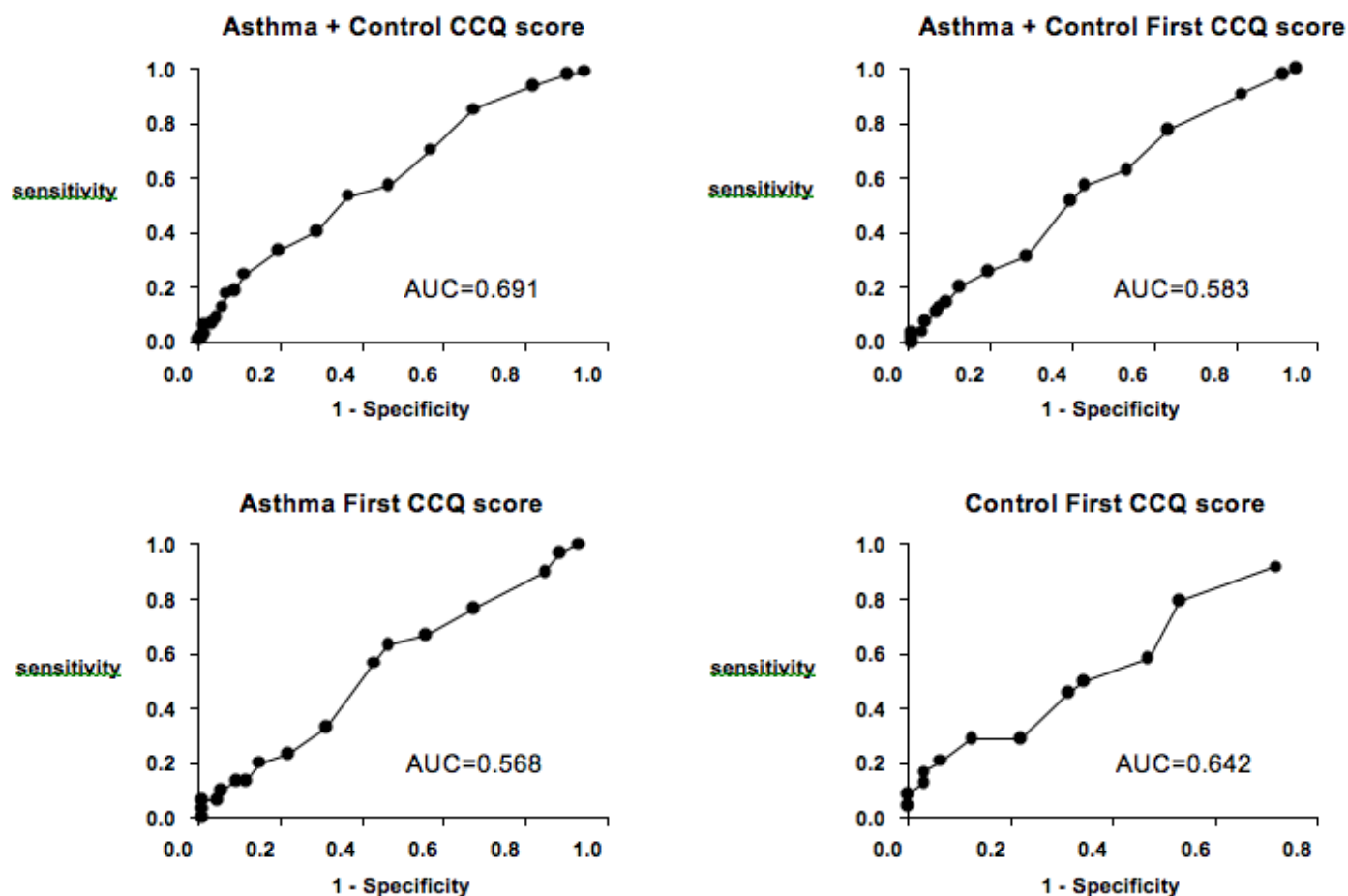


Figure 3. Receiver Operator Curves (ROC) of total common cold questionnaire score and virus result

Respiratory Virus PCR testing

Nasal and throat swabs were collected from women with suspected respiratory viral infection, and viruses identified using real-time quantitative polymerase chain reaction (PCR) using previously described methods⁴. Swab buds were immersed in buffer RLT and stored at -80°C for up to 7 days. Total RNA was extracted and purified using RNeasy RNA mini kit and QIAshredder protocols according to the manufacturer's instructions (Qiagen, Hilden, Germany). RNA was reverse transcribed to cDNA using the high capacity cDNA reverse transcription kit (Applied Biosystems,

Online supplements are not copyedited prior to posting.

Foster City, USA). cDNA from the swabs was used to determine the presence of rhinovirus, enterovirus, respiratory syncytial virus (RSVA and RSVB), influenza A and B, coronavirus and human metapneumovirus. PCR primers and probes were combined with 5 Prime MasterMix (5 Prime Inc, Hamburg, Germany) as per the manufacturer's instructions in singleplex real-time PCRs (7500 Real Time PCR System, Applied Biosystems).

Statistical methods

In order to detect a significantly higher rate of viral infection among pregnant women with asthma (35% ⁵) compared to pregnant women without asthma (10% ⁶), at a power of 0.9 and a, at a power of 0.9 and Cite><Author>Corne</Author><Year>2002</Year><RecNum>4510</RecNum><Disp⁷). In order to allow for drop-outs, we aimed to recruit 70 women per group. However, we recruited more asthmatic women than this because we were recruiting for other studies in tandem ^{1,8}.

We analysed the time to first common cold and first PCR positive cold with Kaplan-Meier plots, with analysis of instantaneous risk described with a Cox proportional hazards model.

CCQ scores were recorded at the first non-cold event (visit or phone call) in order to obtain a baseline for future comparison. Women with asthma had an elevated baseline CCQ score compared to women without asthma due to overlapping symptoms such as sneezing and cough (e-Table 1). At baseline, CCQ scores were significantly different between the asthma and control groups for domains 1, 2 and 4 (e-Table 1).

e-Table 1. Baseline CCQ data

Baseline CCQ	Control n=116	Asthma n=162	P value
Fevers	0 (0,0) range 0-1	0 (0,0) range 0-1	0.821
Chills	0 (0,0)	0 (0,0)	0.017
Muscle pains	0 (0,0) range 0-2	0 (0,0) range 0-2	0.039
Domain 1	0 (0,0) range 0-2	0 (0,0) range 0-2	<0.0001
Watery eyes	0 (0,0) range 0-1	0 (0,0) range 0-3	0.0005
Runny nose	0 (0,0) range 0-2	0 (0,1) range 0-3	0.002
Sneezing	0 (0,1) range 0-2	0 (0,1) range 0-3	0.0001
Domain 2	0 (0,1) range 0-4	1 (0, 2) range 0-9	0.0005
Sore throat (Domain 3)	0 (0,0) range 0-2	0 (0,0) range 0-2	0.040
Cough	0 (0,0) range 0-1	0 (0,1) range 0-3	0.0001
Chest pain	0 (0,0) range 0-2	0 (0,0) range 0-1	0.0001
Domain 4	0 (0,0) range 0-3	0 (0,1) range 0-3	0.0001
Total score	0 (0, 3) range 0-9	3 (0, 6) range 0-20	

Data is median (IQR), range. Analysis by Wilcoxon ranksum test

Results:

Subject characteristics (e-Table 2)

Study participation ended with delivery in the majority of subjects. Completing the study to delivery were 97 control women and 136 asthmatic women. Data from all women commencing the cohort study were included, with adjustments made for follow-up times in each group.

Online supplements are not copyedited prior to posting.

There were no differences between the groups in gestational age at recruitment, number of weeks of follow-up, height, marital status, ethnicity, smoking status, or season of recruitment or study end (P>0.05, e-Table 2). 8.5% of control women and 9.5% of asthmatic women were vaccinated against influenza during the current influenza season.

e-Table 2. Subject characteristics

	Control (n=117)	Asthma (n=168)	P value
Number of weeks in study*	22.1 (19.9, 24.9)	22.0 (18.1, 24.1)	P=0.156
Maternal height (cm)†	165.6 (161, 170) <i>n=116</i>	164 (160, 169.2) <i>n=165</i>	P=0.178
Maternal weight (kg, Visit 1)*	69 (63, 79)	76 (65.9, 88) <i>n=165</i>	P=0.002
Number of children living at home	1 (0, 1) Range 0-3 <i>n=57</i>	1 (0, 2) Range 0-4 <i>n=120</i>	P=0.076
Marital status:‡			P=0.094
Married	66 (61.1%)	77 (47.8%)	
Lives with partner	28 (25.9%)	53 (32.9%)	
Single	14 (13.0%)	31 (19.3%)	
Ethnicity:‡			P=0.302
Caucasian	103 (92.0%)	154 (92.8%)	
Aboriginal/Torres Strait Islander	3 (2.7%)	8 (4.8%)	

Online supplements are not copyedited prior to posting.

Other	6 (5.4%)	4 (2.4%)	
Number of study visits*	6 (5,7)	6 (5, 7)	P=0.075
	Range 1-10	Range 1-10	
	Total study visits = 625	Total study visits = 955	
Number of phone contacts*	6 (4, 7)	5 (4, 6)	P=0.164
	Total calls = 608	Total calls = 832	
<i>Post-bronchodilator spirometry:</i>		<i>n=110</i>	
FEV ₁		3.08 (2.75, 3.38)	
% predicted FEV ₁		97.8 (88.7, 105.9)	
FVC		3.77 (3.34, 4.15)	
% predicted FVC		103.5 (93.6, 113.4)	
ICS treatment		15 (8.9%)	
		10 budesonide	
		5 fluticasone	
ICS/LABA treatment		33 (19.6%)	
		14 budesonide/formoterol	
		19 fluticasone/salmeterol	
<i>Season of recruitment:†</i>			P=0.061
Summer	29 (24.8%)	25 (14.9%)	
Autumn	30 (25.6%)	42 (25%)	
Winter	24 (20.5%)	55 (32.7%)	

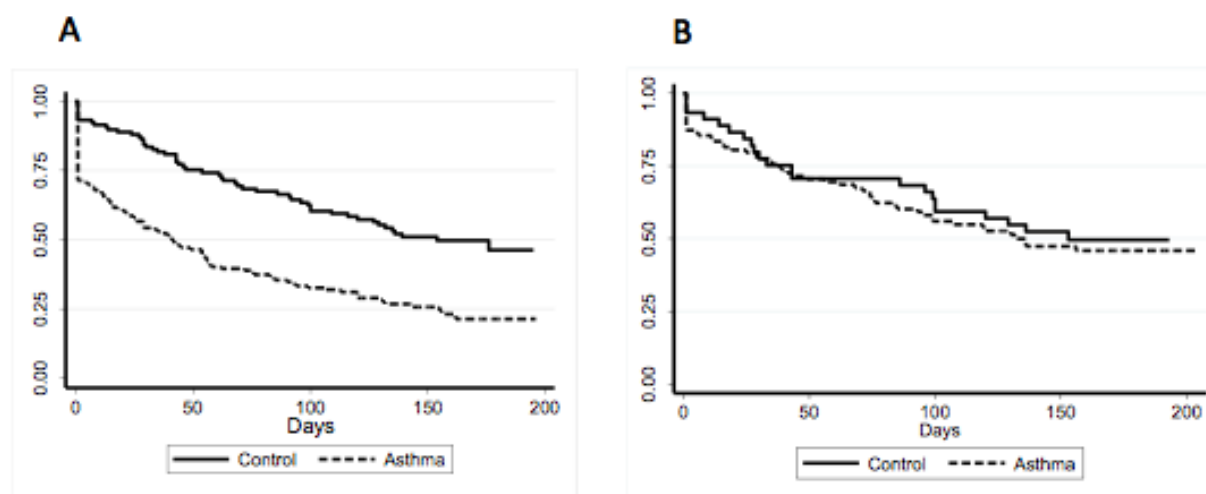
Online supplements are not copyedited prior to posting.

Spring	24 (29.1%)	46 (27.4%)	P=0.133
<i>Season at study end:†</i>			
Summer	26 (22.2)	59 (35.1)	
Autumn	28 (23.9)	35 (20.8)	
Winter	32 (27.4)	36 (21.4)	
Spring	31 (26.5)	38 (22.6)	P=0.677
In study for 3 months of winter‡	19 (16.2%)	25 (14.9%)	

* median (IQR), Wilcoxon ranksum test, †mean (sd), Student’s t-test, ‡n(%), Chi² test.
Seasons were Australian summer (December – February), autumn (March - May), winter (June - August), spring (September – November).

Time to first common cold and first PCR positive cold

We investigated differences in the time to first cold with Kaplan-Meier survival estimates (e-Figure 4). For common colds, the asthma group had a significantly shorter period of study before having their first common cold (hazards ratio 2.27 (1.64, 3.14), P<0.0001), but there was no difference between the groups in the time to first PCR positive cold (hazards ratio 1.14 (0.69,



1.88), $P=0.604$).

e-Figure 4: Kaplan-Meier survival curves for common colds (A) and PCR positive colds (B). Days represents days since study entry.

Frequency of common colds

Approximately 71% of common colds were also considered colds by self-report. Self-reported colds were more likely to be reported by pregnant women with asthma compared to pregnant women without asthma ($P<0.0001$, relative risk [RR] 1.57, 95% confidence interval [CI] [1.24, 1.98]), and the rate was significantly higher when adjusted for follow-up time, atopy, parity and maternal BMI (incidence rate ratio [IRR] 1.66, 95% CI [1.21, 2.29], $P=0.002$).

e-Table 3. Frequency of common colds during pregnancy

	Control (n=117)	Asthma (n=168)
Number of cold events	83	223
Total person weeks	2397	3305
	(46.1 subject years)	(63.6 subject years)
Number of colds in the 2 nd trimester (13-27 weeks)	43 (52%)	145 (65%)
Number of colds in the 3 rd trimester (27-41 weeks)	40 (48%)	74 (33%)
2 nd Trimester colds/person*	0 (0, 1)	1 (0, 1)
3 rd Trimester colds/person*	0 (0, 1)	0 (0, 1)
	P=0.9211	P<0.0001
Person weeks in 2 nd trimester*	10.4 (8.7, 12.4)	10.1 (8.3, 12.0)
Person weeks in 3 rd trimester*	12.6 (11.3, 13.9)	12.3 (9.9, 13.3)
	P=0.0787	P=0.0215
Number of 2 nd trimester colds occurring in winter	13 (30.2%)	49 (33.8%)
Number of 3 rd trimester colds occurring in winter	13 (32.5%)	25 (33.8 %)

* 2nd trimester vs 3rd trimester: Wilcoxon matched-pairs signed-rank test

Online supplements are not copyedited prior to posting.

e-Table 5. Frequency of PCR positive colds during pregnancy

	Control (n=117)	Asthma (n=168)	P value
Common colds tested by PCR of nasal and/or throat swabs	65 (78.3%)	178 (79.8%)	
Number of PCR positive colds	26	60	
Average time since cold worsened at sample collection (individual)*	3.5 (3, 7) days	4 (2, 7) days	P=0.8103
Samples collected within 1-2 days of cold worsening	17/65 (26.2%)	28/178 (15.7%)	
PCR Positive Cold Events	26	60	
PCR+ Cold detected in Nasal Swab	7 (27%)	22 (37%)	
PCR+ Cold detected in Throat Swab	10 (38.5%)	20 (33%)	
PCR+ Cold detected in both Nasal and Throat Swab	9 (34.6%)	18 (30%)	
PCR Positive colds in 2 nd Trimester	15 (57.7%)	37 (62.7%)	
PCR Positive colds in 3 rd Trimester	11 (42.3%)	22 (37.3%)	
	P = 0.4524 (2 nd vs 3 rd Trimester)	P=0.0442 (2 nd vs 3 rd Trimester)	
<i>PCR+ Colds by Season:</i>			
Summer	5 (19.2%)	6 (10%)	

Online supplements are not copyedited prior to posting.

Autumn	8 (30.8%)	15 (25%)
Winter	9 (34.6%)	22 (36.7%)
Spring	4 (15.4%)	17 (28.3%)

Data is n(%) unless stated. *median (IQR), Mann Whitney test

Seasons were Australian summer (December – February), autumn (March - May), winter (June - August), spring (September – November).

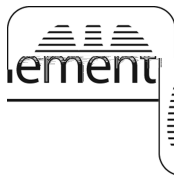
Rhinovirus was the most commonly detected virus in the asthma (38.5% of viruses) and control (44.8% of viruses) groups, followed by metapneumovirus (manuscript Table 3). The odds of having rhinovirus detected was 0.89 (0.33, 2.42 (Odds Ratio (95% CI), p=0.82) in the asthma group compared to the control group.

There were significantly more asthmatic women with retrospectively self-reported colds in the first and second trimester (62%) compared to women without asthma (41%, P=0.0006, RR 1.53, 95% CI [1.19, 1.96], e-Table 5). Women with asthma reported more colds than women without asthma (P=0.0002, Mann Whitney test), and the rate of colds was significantly increased among women with asthma when adjusted for follow-up time, atopy, parity and maternal BMI (IRR 1.64, 95% CI [1.16, 2.32], P=0.005). Similarly, among women followed postpartum (e-Table 5), those with asthma were more likely to retrospectively self-report postpartum colds (67%) compared to women without asthma (43%, P=0.0021, RR 1.57, 95% CI [1.17, 2.11]) and the number of colds reported was significantly greater (P=0.0034, Mann Whitney test).

e-Table 4. Frequency of retrospectively reported colds in early pregnancy (A), and postpartum (B)

(A) Early pregnancy				
	Control (n=116)	Asthma (n=168)	Effect size	P Value
Subjects with self-reported colds since pregnant *	47 (40.5%)	104 (61.9%)	RR 1.528, 95% CI (1.189, 1.963)	P=0.0006
Follow-up time (weeks) †	14.6 (12.6, 16.3)	14.9 (13.0, 16.8)		P=0.225
Number of colds since pregnant †	0 (0, 1) Range 0-2 <i>n=114</i>	1 (0, 1) Range 0-4 <i>n=165</i>		P=0.0002
Total colds since pregnant	50	137		
Total colds per person weeks ‡	50/1696 0.0295	137/2506 0.0547	IRR 1.64, 95% CI (1.16, 2.32)	P<0.005
(B) Postpartum				
	Control group (n=77)	Asthma group (n=95)	Effect size	P Value
Subjects with 1 or more self-reported colds since delivery *	33 (43%)	64 (67%)	Relative Risk 1.57, 95% CI (1.17, 2.11)	P=0.0021
Follow-up time (weeks since delivery) †	27.0 (25.7, 28.6) Range 22.7-34.9	27.5 (25.9, 29.0) Range 22.1 – 40.7		P=0.2934
Number of colds since delivery (among whole	0 (0, 1) Range 0-3	1 (0, 2) Range 0-5		P=0.0034

Online supplements are not copyedited prior to posting.



group) †

Total colds since delivery	48	103	
Total colds per person weeks ‡	48/2098	103/2634	IRR 1.71, 95% CI (1.19, 2.46) P<0.004
	0.0229	0.0391	

Data are median (IQR) unless stated. * n (%), Chi² test, † median (IQR), Mann Whitney test, ‡ Poisson regression adjusted for atopy, parity and BMI.

Severity of common colds

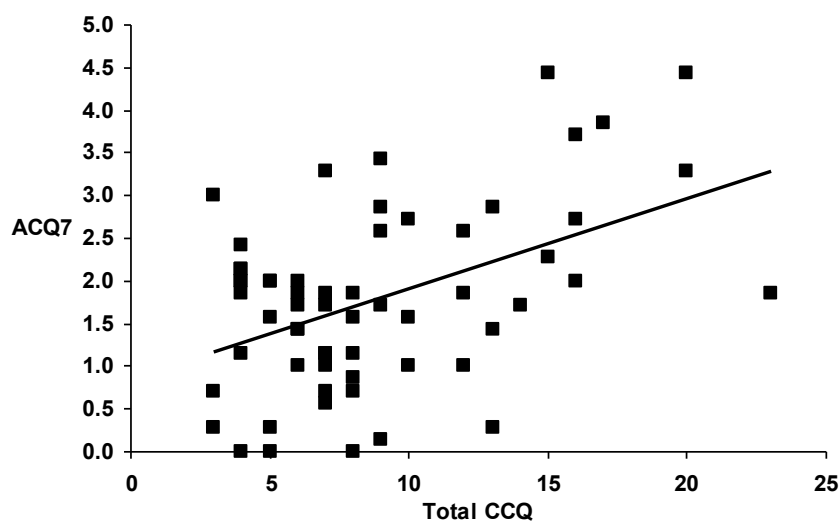
e-Table 6. Severity of Common Cold Events (A) and PCR Positive Cold Events (B)

(A) Common cold events	Control (n=83 events)	Asthma (n=223 events)	P value
CCQ Fevers	0 (0, 0)	0 (0, 0)	
CCQ Chills	0 (0, 0)	0 (0, 0)	
CCQ Muscle Pains	0 (0, 1)	0 (0, 1)	
CCQ Watery Eyes	0 (0, 1)	0.5 (0, 1)	
CCQ Runny Nose	1 (1, 2)	2 (1, 2)	
CCQ Sneezing	1 (1, 2)	1 (1, 2)	
CCQ Sore Throat	1 (1, 2)	1 (0, 2)	
CCQ Cough	1 (1, 2)	2 (1, 2)	
CCQ Chest Pain	0 (0, 0)	0 (0, 1)	
CCQ Total Score *	6 (5, 8)	8 (5, 10)	P=0.031
	Range 3-22	Range 3-22	
CCQ Total Score >=10	13 (15.7%)	63 (28.3%)	

Online supplements are not copyedited prior to posting.

(ACQ > 1.5), with the median ACQ score being 1.8 (1, 2.3). In 50% of events, women used ICS, or ICS/LABA combination therapy, with a median dose of 800 µg/day (IQR 343, 1000, adjusted for self-reported non-adherence).

Among 49 asthmatic women who had a PCR positive cold and a corresponding baseline clinic visit (first non-cold event), the impact of viral infection on asthma was assessed (e-Table 7). There were significantly more exacerbations during PCR positive colds, more uncontrolled asthma, significantly higher ACQ scores and greater symptom burden than during the baseline period. Pre-bronchodilator lung function was significantly lower during PCR positive colds than at baseline for FEV₁ and FVC (e-Table 7). Among 20 control women with a PCR positive cold and a corresponding baseline clinic visit, there was no difference in lung function, but a higher FENO during PCR positive colds (16.2 [12.1, 21.0] vs 6.7 [5.7, 12.0], n=14, Wilcoxon matched-pairs signed-ranks test, P=0.042). PCR positive colds with asthma exacerbation were no more severe (assessed by total CCQ score) than PCR positive colds without asthma exacerbation (xtreg, coefficient 1.42, 95% CI [-1.09, 3.93], P=0.268, e-Table 8). However, PCR positive colds did result in an increase in asthma symptoms, assessed by the ACQ (e-Table 7).



e-Figure 5. Relationship between ACQ score and total CCQ score during PCR positive colds in pregnant women with asthma (Spearman rank correlation $r=0.3187$, $P=0.0131$).

Online supplements are not copyedited prior to posting.

e-Table 7. Impact of PCR positive colds on asthma

	Baseline: no cold (n=49)	First PCR+ Cold (n=49)	P value
Gestational age *	19 (17, 23)	22.4 (18.7, 28.9)	0.0078
<i>Exacerbation events at clinic visit</i>			0.003
Any moderate/severe exacerbation†	2 (4.1%)	17 (34.7%)	
Hospital admission†	0	0	
ED/Labour Ward visit†	0	2 (4.1%)	0.4750
Unscheduled GP visit†	1 (2%)	5 (10.2%)	0.2062
Unscheduled Research study Dr visit †	1 (2%)	10 (20.4%)	0.0105
OCS use†	0	5 (10.2%)	0.0663
Virus infection as self-reported trigger of exacerbation†	0	12 (70.6% of exacerbations)	
Loss of asthma control during probable colds†	14 (28.6%)	15 (30.6%)	0.8249
<i>ACQ7 at clinic visit</i>			
Well controlled asthma (ACQ7<0.75) †	15 (30.6%)	9 (18.4%)	0.2402
Partially controlled asthma (ACQ7 0.75-1.5) †	23 (46.9%)	11 (22.4%)	0.0196
Uncontrolled asthma (ACQ7 >1.5) †	11 (22.4%)	29 (59.2%)	0.0005
Total ACQ7 Score *	0.9 (0.4, 1.4)	1.7 (1.0, 2.0)	<0.0001
ACQ Question 1 (night waking) *	0 (0, 1)	2 (0, 3)	<0.0001

Online supplements are not copyedited prior to posting.

ACQ Question 2 (morning symptoms) *	1 (0, 2)	2 (1, 3)	0.0005
ACQ Question 3 (activity limitation) *	0 (0, 1)	1 (0, 2)	0.001
ACQ Question 4 (shortness of breath) *	2 (0, 2)	2 (1, 3)	0.0191
ACQ Question 5 (wheeze) *	1 (0, 2)	2 (0, 3)	0.0012
ACQ Question 6 (bronchodilator use) *	1 (0, 1)	1 (1, 3)	0.0062
ACQ Question 7 (lung function) *	0 (0, 2)	0 (0, 2)	0.0634
Lung function (pre-bronchodilator)	<i>n=37</i>	<i>n=26</i>	<i>19 pairs</i>
FEV ₁ ‡	3.05 (0.63)	2.93 (0.60)	0.0242
FVC‡	3.84 (0.72)	3.74 (0.71)	0.0442
FEV ₁ :FVC‡	0.80 (0.09)	0.78 (0.09)	0.132
% predicted FEV ₁ ‡	97.9 (15.5)	91.7 (15.2)	0.0241
% predicted FVC‡	107.8 (16.7)	102.3 (17.5)	0.0475
Lung function (post-bronchodilator) <i>n=35</i>	<i>n=29</i>	<i>n=27</i>	<i>16 pairs</i>
FEV ₁ ‡	3.15 (0.58)	2.92 (0.61)	0.7059
FVC‡	3.86 (0.63)	3.66 (0.69)	0.4707
FEV ₁ :FVC‡	0.82 (0.08)	0.80 (0.08)	0.9623
% predicted FEV ₁ ‡	102.6 (14.8)	93.2 (16.4)	0.4544

Online supplements are not copyedited prior to posting.

% predicted FVC†	109.7 (15.0)	101.8 (16.1)	0.2439
FENO (ppb) *	8.2 (4.9, 18.2) <i>n</i> =47	9.5 (5.7, 17.8) <i>n</i> =46	0.9807 (43 <i>pairs</i>)
ECO (ppm) *	2 (2, 4.8) <i>n</i> =42	2 (1, 3) <i>n</i> =42	0.7812 (25 <i>pairs</i>)
<i>Current Treatment</i>			
Beta agonist use (days/week) *	2 (0, 6)	4 (1, 7)	0.0821
Beta agonist use (times/week) *	2 (0, 7)	6 (1, 14)	0.0823
ICS use (either ICS alone or ICS/LABA) †	22 (44.9%)	21 (42.9%)	0.8387
ICS/LABA use†	14 (28.6%)	11 (22.4%)	0.6430
ICS (BDP equivalent dose) µg/day (among users) *	400 (400, 950)	800 (400, 1600)	0.084
ICS (BDP equivalent dose) µg/day (among users) adjusted for self-reported adherence*	343 (132, 686)	686 (400, 800)	0.3054
<i>Symptom Burden</i>			
Night symptoms (days per week) *	0 (0, 2)	2 (1, 5)	0.0012
Morning symptoms (days per week) *	1 (0, 3)	3 (2, 6)	0.0044
Activity limitation (days per week) *	0 (0, 0)	1 (0, 3)	0.0055
Symptom free days (per week) *	5 (0, 7)	1 (0, 5)	0.0367
Nasal VAS *	2.4 (1, 4.8)	5.6 (3, 7.6)	<0.0001
Reflux VAS *	1.1 (0.05, 3.4)	2.7 (0.6, 5.4)	0.0113

Online supplements are not copyedited prior to posting.

Cough VAS *	0.7 (0.1, 2.1)	5.6 (3.5, 6.8) <i>n</i> =32	<0.0001
Asthma VAS*	2.6 (0.7, 4.3)	5 (2.7, 7.3)	0.0005

* median (IQR), Wilcoxon matched-pairs signed-ranks test, † *n* (%) Chi² test, ‡mean (SD) paired *t* test.
ED: emergency department, ACQ7: 7-item asthma control questionnaire, FEV1: forced expiratory volume at 1 second, FVC: forced vital capacity, FENO: fractional exhaled nitric oxide, ICS: inhaled corticosteroid, LABA: long acting beta agonist, BDP: beclomethasone dipropionate, ECO: exhaled carbon monoxide, VAS: visual analogue scale.

e-Table 8. Severity of PCR positive colds with and without asthma exacerbation
ASTHMA GROUP

PCR+ COLDS	No exacerbation (<i>n</i> =40)	Exacerbation (<i>n</i> =20)	P value
Fevers	0 (0, 0)	0 (0, 1)	
Chills	0 (0, 0)	0 (0, 0.25)	
Muscle Pains	0 (0, 1)	1 (0, 1.25)	
Watery Eyes	1 (0, 2)	0 (0, 1.25)	
Runny Nose	2 (1, 2)	2 (0.75, 3)	
Sneezing	2 (1, 2)	1 (0, 2)	
Sore Throat	1 (0.75, 2)	2 (1, 2.25)	
Cough	2 (1, 2)	2 (2, 3)	
Chest Pain	0 (0, 1)	0 (0, 1)	
Total CCQ Score*	7.5 (5.8, 10)	7.5 (5, 15.3)	P=0.268
Total CCQ Score >=10	11 (27.5%)	8 (40%)	
ACQ1 (Night)	1 (0, 3)	2 (1, 3.3)	
ACQ2 (Morning)	2 (1, 3)	2 (2, 3)	

Online supplements are not copyedited prior to posting.

ACQ3 (Activity)	0 (0, 2)	2 (1, 3)
ACQ4 (SOB)	2 (1, 3)	3 (2, 4)
ACQ5 (Wheeze)	2 (0, 3)	3 (2, 3.3)
ACQ6 (Bronchodilator)	1.5 (0, 2.3)	1.5 (1, 3)
ACQ7 (lung function)	1 (0, 2.3)	1 (0, 2.5)
ACQ7 Average	1.4 (0.8, 2.0)	2.0 (1.7, 2.8)

Data is median (IQR) or n(%). * xt reg with adjustment for atopy, parity, BMI and baseline CCQ total score
CCQ: common cold questionnaire, ACQ: asthma control questionnaire

Impact of common colds on neonatal outcomes

In the control group, having one or more common colds during pregnancy did not have a major effect on pregnancy outcomes, with the exception of a higher rate of neonatal hospitalisations among those with common colds (13%) compared to those without common colds in pregnancy (1.6%, $P=0.0391$, Chi square test). Among asthmatic mothers, there was significantly reduced birth length among neonates from asthmatic mothers who had common colds during pregnancy, compared to those who did not ($P=0.016$, Wilcoxon rank-sum test), although this group also had 3 multiple births, compared to only one in the no cold group. There was also no difference in gestational age, birth weight or head circumference, or the rates of preterm delivery or low birth weight ($P>0.05$).

References:

- 1 Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011; 378:983-990
- 2 Powell H, McCaffery K, Murphy VE, et al. Psychosocial outcomes are related to asthma control and quality of life in pregnant women with asthma. *J Asthma* 2011; 48:1032-1040
- 3 Murphy VE, Gibson PG, Talbot PI, et al. Asthma self-management skills and the use of asthma education during pregnancy. *Eur Respir J* 2005; 26:435-441
- 4 Wark PA, Bucchieri F, Johnston SL, et al. IFN-gamma-induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. *J Allergy Clin Immunol* 2007; 120:586-593
- 5 Minerbi-Codish I, Fraser D, Avnun L, et al. Influence of asthma in pregnancy on labor and the newborn. *Respiration* 1998; 65:130-135
- 6 Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002; 359:831-834
- 7 Dupont WD, Plummer WD. PS power and sample size program available for free on the internet. *Control Clin Trials* 1997; 18:274
- 8 Forbes RL, Gibson PG, Murphy VE, et al. Impaired type I and III interferon response to rhinovirus infection during pregnancy and asthma. *Thorax* 2012; 67:209-214

Online supplements are not copyedited prior to posting.