ORIGINAL ARTICLE Lower airways

Respiratory viral infections in pregnant women with asthma are associated with wheezing in the first 12 months of life

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Abstract

Background: There are few studies investigating the relationship between respiratory viral infection in pregnancy and asthma in the offspring, and none among mothers with asthma. Infants of mothers with asthma are more likely to wheeze and have a higher risk of developing asthma than infants of non-asthmatic mothers.
Methods: A prospective cohort study of viral infection in pregnancy was conducted between 2007 and 2009, and a subgroup of infants of mothers with asthma was followed up at 6 and 12 months of age. During common colds, nasal and throat swabs were collected from mothers and respiratory viruses detected by polymerase chain reaction. Respiratory health of infants was assessed by parent-completed questionnaire.
Results: Twelve-month-old infants whose mothers had confirmed viral infections in pregnancy (n = 26) reported more frequent wheeze (40% had 4–12 wheeze attacks compared with 0%), sleep disturbed by wheeze (1 night per week or more in 60% vs. 11%), beta agonist treatment for wheeze (27% vs. 0%), prolonged colds (2 wk or longer 31% vs. 0%), more eczema (40% vs. 6.3%), and parent-perceived asthma (32% vs. 0%), compared with infants whose mothers had common colds without laboratory-confirmed viral infection (n = 16).
Conclusions: This study demonstrates a relationship between maternal respiratory viral infection in pregnancy and wheezing illness in infants of mothers with asthma. Viral infections are the most common cause of asthma exacerbations in pregnancy, and infants of asthmatic mothers are at increased risk of asthma themselves. Further research is needed to elucidate the mechanisms involved.

Asthma is a common comorbid condition in pregnancy, with exacerbations experienced by more than one-third of women (1, 2). The majority of these exacerbations are caused by respiratory viral infection, with one study of pregnant women indicating that self-reported viral infection was the trigger for exacerbation in at least 34% of cases (1). We recently conducted a prospective cohort study of viral infection in pregnancy. Rhinovirus and metapneumovirus were the most common respiratory viruses detected by polymerase chain reaction (PCR) testing in nasal and throat swabs from pregnant women with common cold symptoms (3). Pregnant women with asthma were more likely to report common colds during pregnancy than women without asthma (3). Among women with asthma, having a PCR confirmed common cold was associated with poorer health outcomes, including asthma exacerbations in 30%, uncontrolled asthma in a further 30%, and a higher odds of pre-eclampsia (3). The effect of respiratory viral infection during pregnancy on infant health is yet to be determined.

Pregnancy is a critical time period for exposures, which may alter the developing immune and respiratory systems and influence health in later life. There are many studies showing the link between viral infection in early life and wheezing illness, and it is known that children with recurrent virus-induced wheeze are more likely to develop asthma later in childhood (4–6). However, there are fewer studies examining the role of maternal viral infection during pregnancy on wheezing and subsequent asthma in childhood. Maternal antibodies, antigens, and cytokines are able to pass the feto–placental barrier, and therefore, infections in the mother have

the potential to influence the developing fetus, with consequences for health in later life. In this study, we investigated the association between laboratory-confirmed respiratory viral infections in pregnant women with asthma and wheezing in their infants.

Methods

Study design

Between April 2007 and November 2009, pregnant women with asthma were recruited during their second trimester from the antenatal clinic of John Hunter Hospital, Newcastle, Australia, for a prospective cohort study of viral infection in pregnancy (3). A subgroup (reported in the current study) had completed the pregnancy study, and their infants were followed up at the age of 12 months by a Pediatrician at the John Hunter Children's Hospital (JM). Written informed consent was obtained prior to participation of both mothers and their infants. Ethics approval was granted by the University of Newcastle and Hunter New England Area Health Service Research Ethics Committees (approval number 07/02/21/3.06).

Pregnancy study

Pregnant women with physician diagnosed asthma and asthma symptoms or medication use in the previous 12 months completed monthly clinical assessments and fortnightly telephone calls between visits during which common cold symptoms were investigated using the common cold questionnaire (CCQ) (7). 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] (7). A cold was classified as 'probable' when symptoms were moderate in at least two domains, or mild in at least three domains. Total CCQ score was used to assess severity (possible score 0–27).

During suspected viral infections ('probable cold' according to the CCQ) (3), additional visits were completed either at home or at the hospital. Nasal and throat swabs were collected and tested for common respiratory viral infections (rhinovirus, influenza A and B, respiratory syncytial virus [RSV], human metapneumovirus, coronavirus, and enterovirus) using PCR as previously described (3, 8). Mothers with any virus detected using PCR were described as 'virus-positive mothers', while those whose common colds were not associated with PCR-positive viral infection were described as 'virus-negative mothers'. Further details about the respiratory viral infections in pregnancy can be found in our previous publication (3).

Lung function (EasyOne Spirometer, NicheMedical, North Sydney, Australia) and fractional exhaled nitric oxide (FENO, ECOMEDICS, Duernten, Switzerland, at a controlled flow rate of 50 ml/s) were measured during clinical assessments. Asthma history and severity were assessed at the first visit, while the asthma control questionnaire (9), smoking history and medication use (β_2-agonists, inhaled [ICS], and oral corticosteroids [OCS]) were assessed at each clinic visit by direct questioning using previously described methods (10).

Some of the women with asthma also participated in a randomized controlled trial of FENO-based treatment adjustment vs. clinical guidelines (symptoms/lung function)-based

Table 1 Subject characteristics

	Virus-negative mothers N = 16	Virus-positive mothers N = 26	p-value
Maternal age (years)	27.6 (6.5) Range 19–42	29.1 (6.6) Range 18–41	0.473
Gestational age at recruitment (weeks)	15.8 (2.8) Range 11–21	16.7 (2.4) Range 12–21	0.278
BMI (kg/m^2)	26.3 (21.3, 31.3)	30.3 (25.1, 32.9)	**0.046**
Maternal self-reported smoking during pregnancy	5/16 (31.3%)	4/26 (15.4%)	0.265
Maternal atopy	12/16 (75.0%)	15/26 (57.7%)	0.330
ACQ7	1.3 (0.9)	1.1 (0.7)	0.238
ICS treatment	7/16 (43%)	4/26 (15%)	0.070
FENO (ppb)	19.1 (16.5, 29.1)	8.0 (5.1, 26.3)	0.578
Pre-bronchodilator FEV_1 (L)	3.01 (0.46) n = 14	3.10 (0.62) n = 22	0.658
% Predicted FEV_1	93.2 (14.3)	99.2 (16.5)	0.230
Pre-bronchodilator FVC (L)	3.9 (0.5) n = 14	3.9 (0.7) n = 22	0.705
Pre-bronchodilator FEV_1/FVC	0.78 (0.06)	0.79 (0.09)	0.736
Gestational age at first common cold (weeks)	21 (15.7, 24.7) Range 12.7–39.6	25.2 (20.0, 29.7) Range 12.9–38.3	
CCQ Score at first common cold	7.5 (6, 8.3)	7.5 (5.3, 9)	

Values are mean (SD) or median (IQR) or n (%).

BMI, body mass index at recruitment; ACQ7, 7-item Asthma Control Questionnaire; CCQ, common cold questionnaire; ICS, inhaled corticosteroid; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity. Bold text highlights the significant values (P<0.05).

treatment adjustment known as the Managing Asthma in Pregnancy (MAP) study (11, 12). Some women also donated blood for *in vitro* studies of responses to viral infection (13–15).

Infant follow-up

Infants underwent a clinical examination and parent interview at approximately 6 and 12 months of age with a specialist Respiratory Paediatrician (JM), which focused on the upper and lower respiratory system, skin, and cardiovascular system. Infant weight, length, and head circumference were measured. The interview obtained information about infant medical history (wheeze, bronchiolitis, physician diagnosed asthma, medication use, and healthcare utilization), immunizations, breast-feeding history, and age of reaching developmental fine and gross motor, language, and social interaction milestones.

Parents (mostly mothers) completed a validated and standardized questionnaire with 50 questions on patterns of wheeze and other respiratory symptoms, respiratory infections, socioeconomic status, family history of allergic diseases, breastfeeding, immunization, and housing (16).

Statistical analysis

Analysis was conducted using STATA 11 (StataCorp, College Station, TX, USA). Data were compared by the mother's viral infection during pregnancy (PCR positive vs. PCR negative) using a chi-square or Fisher's exact tests as appropriate. Continuous data were compared using a Wilcoxon rank-sum test for nonparametric data. A p-value of <0.05 was considered statistically significant, and the Bonferroni correction factor utilized for multiple comparisons.

Table 2 Detection of respiratory viral infections in pregnancy by polymerase chain reaction

Virus	Number of detections
Rhinovirus	14
Coronavirus	6
Human metapneumovirus	4
Enterovirus	3
Influenza A	1
Influenza B	1
Respiratory syncytial virus A	1
Respiratory syncytial virus B	1

Results

Subject characteristics of mothers with asthma (Table 1)

A total of 42 mothers with asthma had infants who underwent clinical assessments at 12 months of age. A total of 26 of the mothers had PCR-positive respiratory viral infections recorded during pregnancy, while 16 had PCR-negative common colds in pregnancy. Virus-positive mothers had a significantly greater body mass index (BMI) at recruitment than virus-negative mothers (30.3 vs. 26.3, $p = 0.046$), but there were no other significant differences in maternal age, smoking status, atopy, asthma control, or lung function between the groups (Table 1).

Table 3 Infant characteristics at 12 months of age

	Virus-negative mothers N = 16	Virus-positive mothers N = 26	p-value
Male infant	5 (31.3%)	13 (50%)	
Age of infant at assessment (months)	12.6 (0.8)	12.5 (0.5)	0.476
Weight (kg)*	10.2 (1.7)	9.5 (1.1)	0.087
Height (cm)*	76.9 (3.8)	75.2 (3.4)	0.130
Heart rate (beats per minute)*	136 (9)	133 (15)	0.728
Respiratory rate (breaths per minute)†	36 (36, 48)	38 (36, 44)	0.821
Head circumference (cm)†	46.3 (45.4, 47.5)	46.0 (45.0, 47.3)	0.649
Currently breastfed	3/14 (21.4%)	7/24 (29.2%)	0.715
Bronchiolitis in past year‡	5/17 (29.4%)	6/25 (24.0%)	0.695
Asthma diagnosis by Dr	0/17	1/26 (3.8%)	1.0
Number of siblings†	0 (0, 0)	0 (0, 1)	0.787
Age smiled (weeks)†	4.5 (2.5, 6.0)	6.0 (3.5, 6.5)	0.343
Age rolled (months)†	4.8 (4.0, 5.0)	4.0 (3.3, 5.5)	0.455
Age sat (months)*	7.0 (1.8)	5.9 (1.1)	**0.021**
Age crawled (months)*	7.3 (2.0)	7.4 (2.0)	0.844
Age walked (months)*	10.9 (1.2)	10.6 (1.3)	0.696
Age words (months)*	8.4 (2.8)	8.2 (2.0)	0.773
Snoring	4/17 (23.5%)	9/24 (37.5%)	0.499
Sleep concerns	3/17 (17.7%)	2/26 (7.7%)	0.369
Obstructive sleep apnea	1/16 (6.3%)	0/22 (0%)	0.421
Eczema	3/17 (17.7%)	10/26 (38.5%)	0.187

Values are n/N(%), Fisher's exact test; ‡chi-square test; *mean (sd), Student's *t*-test; †Median (IQR), Wilcoxon rank-sum test. Bold text highlights the significant values ($P<0.05$).

Table 4 Infant respiratory health at 6 and 12 months of age

	6 months			12 months		
	Virus-negative mothers N = 15	Virus-positive mothers N = 22	p-value	Virus-negative mothers N = 16	Virus positive mothers N = 26	p-value
Wheeze ever*	6/15 (40%)	12/22 (55%)	0.385	9/16 (56.3%)	14/26 (53.9%)	0.879
Wheeze past 6/12 months*	6/15 (40%)	12/22 (55%)	0.385	9/16 (56.3%)	15/26 (57.7%)	0.927
In past 12 months: wheeze during cold	5/6 (83%)	10/12 (83%)	1.0	8/9 (88.9%)	15/16 (93.8%)	1.0
In past 12 months: wheeze without cold	1/6 (17%)	6/12 (50%)	0.171	1/9 (11.1%)	6/16 (37.5%)	0.355
In past 12 months: number of wheeze attacks						
None	0/6 (0%)	0/12 (0%)	0.529	0/9 (0%)	3/15 (20%)	**0.011**
1–3	5/6 (83%)	7/12 (58%)		9/9 (100%)	6/6 (40%)	
4–12	1/6 (17%)	4/12 (33%)		0/9 (0%)	6/6 (40%)	
>12	0/6 (0%)	1/12 (8%)				
Does wheeze cause shortness of breath						
Always	1/6 (17%)	1/12 (8.3%)	0.596	1/9 (11.1%)	1/13 (7.7%)	0.065
Occasionally	3/6 (50%)	4/12 (33.4%)		2/9 (22.2%)	9/13 (69.2%)	
Never	2/6 (33%)	7/12 (58.3%)		6/9 (66.7%)	3/13 (23.1%)	
Sleep disturbed by wheezing						
Never	3/6 (50%)	6/12 (50%)	1.0	8/9 (88.9%)	6/15 (40%)	**0.033**
<1 night/wk	2/6 (33%)	4/12 (33%)		1/9 (11.1%)	9/15 (60%)	
≥1 night/wk	1/6 (17%)	2/12 (17%)		0/9 (0%)	0/15 (0%)	
In past 12 months: wheeze interfere with activities						
Not at all	4/6 (66.7%)	8/12 (66.7%)	0.392	7/9 (77.8%)	8/16 (50%)	0.486
A little	1/6 (16.7%)	2/12 (16.7%)		2/9 (22.2%)	7/16 (43.8%)	
Moderate	0/6 (0%)	2/12 (16.7%)		0/9 (0%)	1/16 (6.2%)	
A lot	1/6 (16.7%)	0/12 (0%)				
In past 12 months: do you think your child had asthma?	2/15 (13.3%)	4/21 (19%)	0.650	0/14 (0%)	8/25 (32%)	**0.034**
In past 12 months: did your child suffer ruttles?						
Never	4/15 (26.7%)	6/22 (27.3%)	**0.008**	4/16 (25%)	4/25 (16%)	0.160
Only with a cold	10/15 (66.7%)	7/22 (31.8%)		11/16 (68.8%)	12/25 (48%)	
Sometimes	0/15 (0%)	9/22 (40.9%)		1/16 (6.3%)	8/25 (32%)	
Even without a cold	1/15 (6.7%)	0/22 (0%)		0/16 (0%)	1/25 (4%)	
Almost always	0/15 (0%)	0/22 (0%)		0/16 (0%)	0/25 (0%)	
Posset/vomit						
Not at all	0/15 (0%)	1/22 (4.5%)	0.544	5/16 (31.3%)	1/26 (3.9%)	**0.030**
A little	11/15 (73.3%)	13/22 (86.7%)		9/16 (56.3%)	16/26 (61.5%)	
A lot	4/15 (26.7%)	8/22 (36.4%)		2/16 (12.5%)	9/26 (34.6%)	
Bronchiolitis						
Never	13/15 (86.7%)	20/22 (90.9%)	0.461	11/16 (68.8%)	19/26 (73.1%)	0.451
Once	2/15 (13.3%)	1/22 (4.5%)		5/16 (31.3%)	5/26 (19.2%)	
>Once	0/15 (0%)	1/22 (4.5%)		0/16 (0%)	2/26 (7.7%)	
Croup						
Never	14/15 (93.3%)	21/22 (95.5%)	0.341	14/16 (87.5%)	22/26 (88.0%)	1.0
Once	0/15 (0%)	1/22 (4.5%)		1/16 (6.3%)	2/26 (8.0%)	
>Once	1/15 (6.7%)	0/22 (0%)		1/16 (6.3%)	1/26 (4.0%)	
In past 12 months: eczema	0/15 (0%)	2/22 (9.1%)	0.230	1/16 (6.3%)	10/25 (40.0%)	**0.028**
Number of colds/flu						
Never	1/15 (6.7%)	3/21 (14.3%)	0.656	0/16 (0%)	0/26 (0%)	0.462
1–3	12/15 (80%)	14/21 (66.7%)		7/16 (43.8%)	16/26 (61.5%)	
4–6	2/15 (13.3%)	4/21 (19.0%)		6/16 (37.5%)	8/16 (30.8%)	
7–10	0/15 (0%)	0/21 (0%)		2/16 (12.5%)	2/26 (7.7%)	
>10	0/15 (0%)	0/21 (0%)		1/16 (6.3%)	0/26 (0%)	

Table 4 (Continued)

	6 months			12 months		
	Virus-negative mothers N = 15	Virus-positive mothers N = 22	p-value	Virus-negative mothers N = 16	Virus positive mothers N = 26	p-value
Length of cold						
<1 wk	10/15 (75%)	8/18 (44.4%)	0.348	4/15 (26.7%)	9/26 (34.6%)	**0.032**
1–2 wk	5/15 (25%)	9/18 (50%)		11/15 (73.3%)	9/26 (34.6%)	
2–4 wk	0/15 (0%)	1/18 (5.6%)		0/15 (0%)	7/26 (26.9%)	
>4 wk	0/15 (0%)	0/18 (0%)		0/15 (0%)	1/26 (3.9%)	
In past 12 months: * sneezing/ blocked nose without cold	5/15 (33.3%)	15/22 (68.2%)	**0.037**	5/16 (31.3%)	13/26 (50%)	0.233
In past 12 months, wheeze or asthma caused						
Consultant visit	1/15 (6.7%)	2/22 (9.1%)	0.791	1/16 (6.3%)	3/26 (11.5%)	1.0
Hospital admission	1/15 (6.7%)	0/22 (0%)	0.220	1/16 (6.3%)	0/26 (0%)	0.381
Emergency department visit	3/15 (20%)	2/22 (9.1%)	0.341	3/16 (18.8%)	6/26 (23.1%)	1.0
GP emergency visit	2/15 (13.3%)	0/22 (0%)	0.078	3/16 (18.8%)	4/26 (15.4%)	1.0
β_2-agonist treatment	0/14 (0%)	0/22 (0%)	1.0	0/16 (0%)	7/26 (26.9%)	**0.033**
Inhaled corticosteroid treatment	0/14 (0%)	0/22 (0%)	1.0	0/16 (0%)	1/26 (3.9%)	1.0
Oral steroid treatment	1/14 (7.1%)	1/22 (4.5%)	0.740	2/16 (12.5%)	4/26 (15.4%)	1.0

Numbers are n/N (%), Fisher's exact test, * Chi square test. Bold text highlights the significant values (P<0.05).

Viral infections during pregnancy (Table 2)

Among the 26 mothers with PCR-detected viruses, there were 31 viruses detected (Table 2). The majority of women had rhinovirus (14/26) while coronavirus and metapneumovirus were the next most frequent infections. First infections occurred from 12.9 to 38.3 wk gestation (median 25.2 wk, interquartile range 20.0, 29.7 wk). Two women had PCR-positive viruses on two occasions (both separated by >10 wk; rhinovirus then influenza B, and metapneumovirus then rhinovirus), while three women had multiple viruses detected in a single sample collection (rhinovirus and enterovirus, rhinovirus and coronavirus, rhinovirus and RSVA).

Infant characteristics at 12 months of age (Table 3, Table S1)

Infant characteristics were obtained by parental interview with the Pediatrician, and by Pediatrician clinical assessment. There were no significant differences between the groups in infant weight, height, or head circumference at 12 months of age. All infants were fully immunized up until 6 months, and many (>40%) had also received their 12-month immunizations at the time of the study visit. Less than 30% of infants were currently breastfed. Developmental milestones and health were generally normal and not significantly different between the groups, with the exception of age at sitting, which was significantly earlier in infants with virus-positive mothers (Table 3).

Infant respiratory health at 12 months of age (Table 4, Table S2)

Infant health was assessed by parent-completed questionnaire. Compared with 12-month-old infants from mothers with asthma and PCR-negative common colds during pregnancy, infants from mothers with asthma who had PCR-positive respiratory viral infections in pregnancy had more frequent wheeze (p = 0.011), more sleep disturbed by wheezing (60% had sleep disturbed by wheezing 1 night per week or more vs. 11%, p = 0.033), more β_2-agonist treatment for wheeze (27% vs. 0%, p = 0.033), more parent-perceived asthma (32% vs. 0%, p = 0.034), more frequent possetting (96% posset/vomit a little or a lot vs. 69%, p = 0.03), more frequent eczema (40% vs. 6.3%, p = 0.028), and more prolonged colds (31% had colds lasting 2 wk or more vs. 0%, p = 0.032, Fig. 1, Table 4). However, there were no significant differences between the groups in the proportion of infants with bronchiolitis, croup, or other medical interventions for wheezing (such as general practitioner or emergency department visits or hospitalization), or in the parent-reported number of colds experienced in the first 12 months (Table 4 and Table S2).

Among the infants who were assessed at 12 months of age who also had an assessment at 6 months of age, these relationships were not apparent (Table 4). However, at 6 months of age, infants in the virus-positive group (total n = 22) were more likely to have had rattly breathing (ruttles, p = 0.008) compared with infants in the virus-negative group (total n = 15, Table 4).

Discussion

The results of this study showed an association between confirmed maternal respiratory viral infection in pregnancy and wheezing illness in infancy. Infants whose mothers had laboratory-confirmed viral infections had more frequent wheeze, more sleep disturbed by wheezing, more β_2-agonist treatment for wheeze, more parent-perceived asthma, more

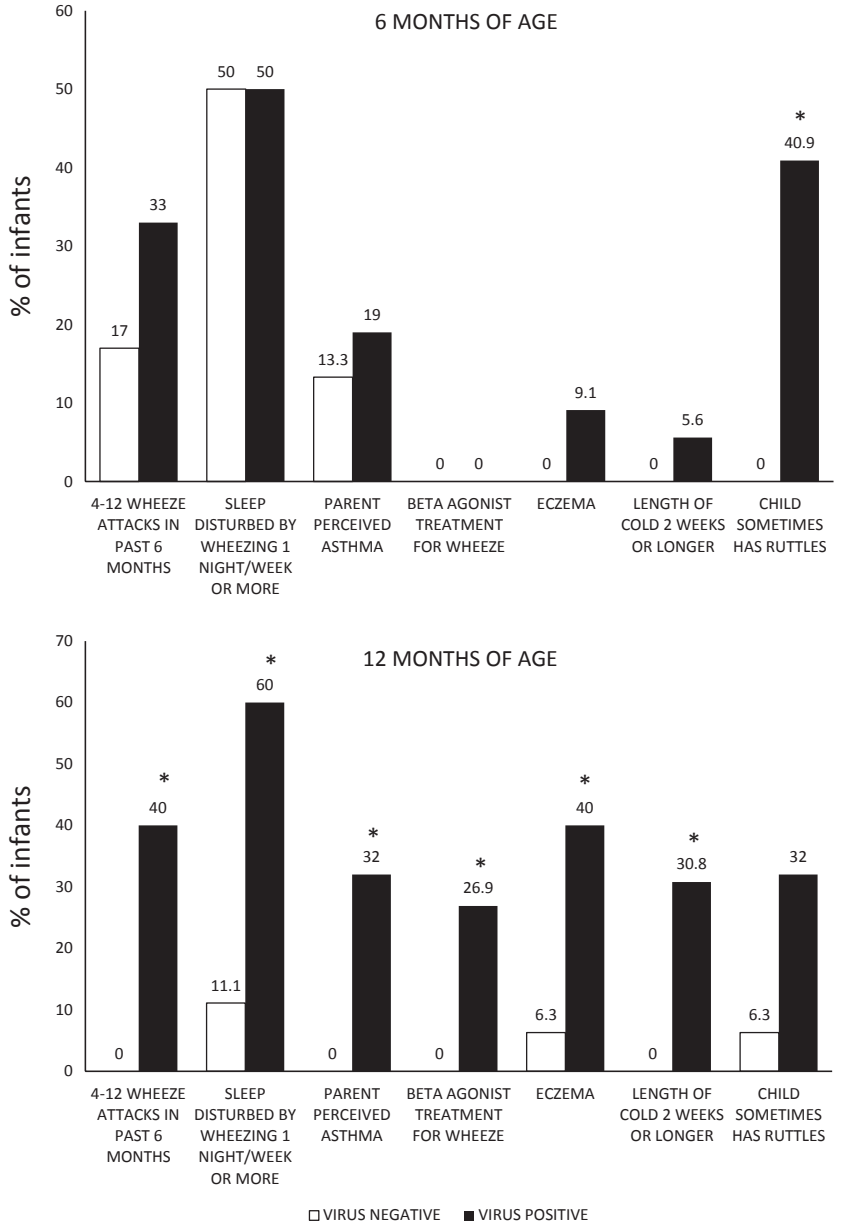

Figure 1 Parent-reported health characteristics of infants and 6 and 12 months of age according to maternal viral infection during pregnancy (*indicates significant results, $p < 0.05$).

frequent posseting, more frequent eczema, and more prolonged colds than 12-month-old infants whose mothers did not have laboratory-confirmed viral infections. At 6 months of age, a relationship between maternal viral infection and rattly breathing was apparent, but wheezing and other wheeze-related outcomes were not significantly different between groups. There was no association observed between maternal viral infection in pregnancy and parent-reported bronchiolitis or croup in infancy, or the number of colds experienced in infancy.

Infants of mothers with asthma are more likely to wheeze than those without a maternal history of asthma. In our cohort, more than half of all infants had wheezed in the first 12 months of life. At 6 months of age, 48.6% of all infants had wheezed, while at 12 months of age 57% had ever wheezed. Asthma develops in one of every six children in Australia and is the most common chronic disease leading to disability in childhood (17). A maternal as opposed to a paternal history of asthma is thought to confer the single greatest risk for development of allergic asthma in the offspring (18). Epidemiological studies aimed at further elucidating the relationship between genetic and environmental factors associated with maternal asthma and the subsequent development of allergic asthma in early life have mostly produced indirect evidence for a complex gene–environmental interaction facilitating a predominant role of maternal asthma during pregnancy for the development of subsequent asthma in the offspring (19). For example, maternal imprinting of 'asthma genes' after

conception (20), intra-uterine infections leading to distorted immune responses at the feto–maternal interface (21), previous pregnancies and exposure to children during pregnancy (22), placental dysfunction leading to low birth weight, premature labor, and subsequent prematurity (23), and intra-uterine smoke exposure (24, 25) have all been linked to an altered risk for the development of asthma in early life. Some of those risk factors (e.g., low birth weight) have also been associated with maternal asthma exacerbations during pregnancy in independent cohorts (26). A direct relationship between maternal asthma during pregnancy (its severity, control, and management) and subsequent asthma risk in the offspring has yet to be established prospectively.

Acute wheezing in early life is often associated with respiratory viral infections, such as rhinovirus or RSV, leading to an increased risk of ongoing childhood wheeze (27), but may also occur in the absence of clinically apparent viral illness. Expiratory flow limitation during wheezing may result from acute airway narrowing associated with bronchoconstriction and/or mucosal edema. Events such as these during a critical period of lung development may have significant effects throughout the airway tree and consequences for health in later life.

One previous study has investigated viral infection in pregnant mothers and the risk of wheeze and atopy in the offspring at 18 months of age (28). In this study from the Danish National Birth Cohort, mothers employed in childcare institutions were presumed to be highly exposed to infections during pregnancy, while mothers not employed in childcare were not. Among first born infants only, having a mother who worked in childcare institutions during pregnancy increased the risk of recurrent wheeze by 37% (adjusted hazard ratio 1.37, 95% confidence interval [1.05–1.77]) compared with firstborn infants of mothers who were not employed in childcare institutions (28). These data are consistent with our study findings, which demonstrate an association between maternal infection during pregnancy and increased risk of infant wheeze.

A case–control study of 200 children with asthma (5–16 yr of age) investigated respiratory tract infections in their mothers during pregnancy using primary care records (29). There was a significant association between respiratory tract infections in pregnancy and asthma in childhood (OR 1.69, 95% CI 1.05, 2.77) which was strongest for infections in the first trimester, and related to the number of infections recorded (29). Similar data were reported by Calvani et al. (30) in 2004, among 338 children with asthma whose mothers were asked about 'flu episodes' and 'fever episodes' during pregnancy by questionnaire. The odds of asthma in children (>3 yr old) was significantly increased when mothers reported flu episodes (adjusted OR 1.91, 95% CI 1.1, 3.2) or fevers in pregnancy (adjusted OR 2.16, 95% CI 1.2, 3.9). In particular, flu episodes in the third trimester increased the risk of asthma by more than sixfold (adjusted OR 6.7, 95% CI 1.33, 33); however, most mothers reported episodes only in one trimester, suggesting they were most likely recalling their worst episode (30). Our prospectively collected data are consistent with this previous work, in demonstrating an association between maternal respiratory viral infection and wheeze in infancy.

While our study has the advantage of having tested swabs for viral infection in the laboratory, there were also several limitations. The viral causes of infant wheezing were not investigated in this study, and although infants whose mothers had respiratory viral infections in pregnancy had more wheeze, this did not translate into more bronchiolitis, croup, or hospitalization. The infants whose mothers had infections in pregnancy were more likely to be treated for wheeze with beta agonists, suggesting an increase in wheezing of more mild severity. There is the possibility of recall bias from parents or misclassification of wheeze by parents and the possibility of missed infections in the virus-negative mothers. In addition, we do not have data on baseline infections (in the absence of clinical symptoms of a common cold) for all pregnant women, so the possibility of colonization by viruses contributing to positive detections in pregnancy is possible. However, we have previously noted that women who respond negatively to the CCQ are unlikely to be PCR-positive to virus (3). Maternal BMI was significantly different between the groups, and this may have influenced the results we observed since maternal BMI has been reported as an independent risk factor for wheeze in the offspring's first 7 yr of life (31). It is also possible that passive smoke exposure was an unmeasured confounder of the results.

In summary, respiratory viral infection during pregnancy has the potential to influence the developing fetus and, in this study, was associated with an increase in the frequency and severity of wheeze at 12 months of age. It is not known whether maternal viral infection induces an abnormal fetal immune response, which contributes to asthma later in life. Further investigations during pregnancy and infancy are needed to elucidate the mechanisms involved.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Infant characteristics at 12 months of age.

Table S2. Results of questionnaire for infants of asthmatic mothers at 12 months of age.