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Febrile respiratory illnesses in infancy & atopy are risk factors for persistent asthma & wheeze.

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Abstract

Background
Severe viral respiratory illnesses and atopy are risk factors for childhood wheezing and asthma.

Objective
To explore associations between severe respiratory infections and atopy in early childhood with wheeze and asthma persisting into later childhood.

Methods
147 children at high atopic risk were followed from birth to 10years. Data on all respiratory infections occurring in infancy were collected prospectively and viral etiology ascertained. Atopy was measured by skin prick tests at 6months, 2 and 5years. History of wheeze and doctor-diagnosed eczema and asthma was collected regularly until 10years of age.

Results
At 10years 60% of the cohort was atopic, 25.9% had current eczema, 18.4% current asthma and 20.4% persistent wheeze. 35.8% experienced ≥one lower respiratory infection (LRI) associated with fever and/or wheeze in year1. Children who had wheezy, or in particular, febrile LRI in infancy and were atopic by 2years, were significantly more likely to have persistent wheeze (RR3.51; 95%CI 1.83-6.70; $p<0.001$) and current asthma (RR4.92; 95%CI 2.59-9.36; $p<0.001$) at 10years.

Conclusion
Severe viral respiratory infections in infancy and early atopy are risk factors for persistent wheeze and asthma. The strongest marker of the asthmatogenic potential of early life infections was concurrent fever.

Word count (193)

Capsule Summary

The occurrence of fever during respiratory illnesses is an important marker of risk for wheeze and asthma later in childhood, suggesting it should be measured in prospective studies of asthma aetiology.

Keywords: Asthma, atopy, febrile infections, persistent wheeze, severe respiratory infections

Background

Asthma in children remains the most common cause of emergency room visits and hospitalisation[1]. Despite intense research, asthma prevention strategies remain elusive, in part because of its genetically complex and heterogeneous nature which has several clinical phenotypes[2, 3]. Although all phenotypes of childhood wheezing are of concern, persistent asthma and wheeze carries the heaviest toll on both the individual and healthcare resources. Thus, the early and precise identification of children at risk of persistent asthma and wheeze is necessary if early intervention strategies are to be effective.

Multiple risk factors for persistent wheeze and asthma have been identified including allergic rhinitis, eczema and atopy, particularly when sensitisation occurs early in childhood[4]. One of the strongest risk factors appears to be viral respiratory infections which are common in early childhood and frequently associated with wheezing symptoms and subsequent asthma diagnosis[5]. Respiratory syncytial virus (RSV)-associated lower respiratory illnesses (LRI) have been reported to be risk factors for frequent wheeze in early childhood, especially in those requiring hospitalisation, but this risk diminished with increasing age[6].

Previously, RSV and human metapneumovirus (HMPV) have been implicated as major etiologic agents for LRI[7, 8], but human rhinoviruses (HRV) are gaining recognition as significant LRI pathogens[9-13]. Infants hospitalised for HRV-induced wheezing in infancy were found to have increased risk of asthma at 6years in one of the first studies to report HRV as inducers of early childhood wheezing[9]. A cohort of 118 infants hospitalised for wheezy illnesses found HRV-

associated wheezing was a significant risk factor for recurrent wheezing[10]. The oldest child at outcome was 35months and further followup will determine whether the wheezing persists. Lemanske et al investigating a high risk cohort found HRV-wheezing illnesses in infancy was associated with preschool wheezing[11]. Similarly, HRV or RSV-associated wheeze in the first 3years of life were associated with asthma at 6years[12]. Patterns of wheezy illnesses appear to be set by 6years and do not appear to change at 16years in children presenting with asthma-like symptoms early in life[14].

Evidence is accumulating that these risk factors do not act alone, with the highest risk for development of persistent asthma observed in children who experience both early atopic sensitisation and severe LRIs during infancy[5]. In this context, we have previously demonstrated that children who experienced HRV or RSV-associated LRI in year1 were more likely to report current wheeze and asthma at 5years, and this effect was confined to children who were sensitized by 2years[15].This high risk cohort has recently completed their 10year follow-up, and we report the effects of respiratory illnesses in the first year and early atopic sensitization on the persistence of wheeze and asthma to10years.

Methods

The study subjects were the 147 (74.2%) children who completed the 10year assessment from the 198 infants seen at 5yrs of age in a prospective birth cohort previously described[15]. The children who were at high risk of atopy (at least one parent with doctor-diagnosis of eczema, hay fever or asthma), were recruited and followed from birth until 10years of age. Close follow-up of all respiratory illnesses were performed through daily diary to record symptoms of acute respiratory illnesses (ARI) and fortnightly follow-up telephone calls until resolution of symptoms. The diary recorded symptom duration including runny/blocked nose, fever (temperature >38˚C – taken with digital thermometers), cough and wheeze. These data were confirmed during follow-up calls and information about any physician visit and doctor diagnoses. Home visits to collect nasopharyngeal aspirates (NPA) were performed within 48hours of illness notification. NPAs including two control samples (one taken in winter and another in summer when the child was well), were frozen at -80^{o}C and subsequently analysed by reverse transcriptase polymerase chain reactions (PCR) for human rhinoviruses (HRV), other picornaviruses (coxsackie, echo and enteroviruses), RSV, influenza A and B, coronaviruses 229E and OC43, parainfluenza viruses 1-3, adenoviruses, human metapneumovirus (HMPV), *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* as previously described[16].

Atopy was determined by skin prick tests (SPT) at 6months, 2, 5 and 10years to a panel of 7 allergens (cow's milk, eggwhite, ryegrass, alternaria, aspergillus, housedustmite, and cat dander). Histamine was the positive control and normal saline the negative control. Wheal size

was read after 15minutes and wheal ≥2mm (for tests at 6months and 2years), ≥3mm (at 5 and 10years) greater than saline control, considered positive. Similar SPT were performed on the parents and wheal size ≥3 mm considered positive.

Classification of Acute Respiratory Illnesses (ARI)

Episodes of ARI were classified as Upper and Lower Respiratory Illnesses based on information derived from diary cards and telephone contacts.

Upper respiratory tract illness (URI)

URI - episodes of runny/blocked nose or cough in absence of other respiratory symptoms (no tachypnoea, difficulty breathing, wheeze or rattly chest).

Lower respiratory tract illness (LRI)

LRI - episodes associated with wheeze or rattly chest and/or evidence of respiratory distress. Rattle/rattly chest was defined as moist, wet noisy breath sounds from child's chest and wheeze as audible, expiratory, high-pitched whistling sounds from parental or doctor's report. Because wheeze is not easy to recognize, episodes were verified with the study doctor or family physician (46% of ARI were seen by family physician). LRI were classified as wheezy LRI and non-wheezy LRI based on the presence of wheeze.

Febrile acute respiratory illness (Febrile ARI)

Febrile infections -ARI associated with fever (temperature >38˚C on two occasions >1hour apart in previous 48hours).

Febrile lower respiratory illness (Febrile LRI)

Episodes of LRI with fever

Definitions

Persistent wheeze - wheeze occurring between 0-3yrs & continuing in the 12months preceding 10year visit.

Asthma – doctor-diagnosis of asthma ever.

Current asthma – asthma and persistent wheeze or asthma medication in preceding12months.

Eczema – doctor-diagnosis of eczema ever

Current eczema – eczema in preceding 12months

Log-binomial regression models were used to estimate risk ratios for persistent wheeze and current asthma at 10years. Multivariate models were adjusted for gender, breastfeeding, pet ownership, older siblings, second-hand tobacco smoke exposure and daycare attendance. All analyses were done using STATA version 11.0 (Stata Corporation, College Station, Texas, US). P-values <0.05 were considered statistically significant.

Current data from 147 children (with approximately 20% with current asthma and persistent wheeze at 10years) will provide 80% power to detect a relative risk of 2.1 or higher at 0.05 level of significance for association with current asthma (or persistent wheeze) for a risk factor with greater than 20% prevalence.

The ethics committee of King Edward Memorial and Princess Margaret Hospitals in Western Australia gave approval and fully informed parental consent was obtained for all subjects.

Results

Cohort characteristics

147 (74.78%) of the 198 children who were seen at 5years completed this 10year follow-up. No significant differences were found in prevalence of atopy or wheeze/asthma at 5years in the children who were seen at the 10year follow-up compared to those who were not involved in this visit. (Information on cohort size and followup numbers - in online supplement).

The majority of the cohort was male (57.8%). 38.8% attended daycare in year1. Only 5 (3.4%) were exposed to maternal smoking in utero and 12.9% to second-hand smoke in the 10years. Prevalence of parental atopic disease was high, with hay fever and asthma the more common conditions reported. 83.0% of fathers and 82.3% of mothers were atopic, and 68.7% of the cohort had biparental atopy. 69.4% of the children were breastfed for >26weeks.

Prevalence of atopic conditions

49.0% reported doctor-diagnosis of allergic rhinoconjunctivitis (ARC) (Table 1). Seventy seven (52.4%) had eczema ever and 25.9% current eczema (Table 1). 59.9% were atopic (food and aeroallergen sensitisation reported in online supplement). 36.1% had been diagnosed with asthma (Table 1). Of these, 27 (50.9%) had current asthma at 10years and 56.6% (30/53) had persistent wheeze. 66.7% of children with both current asthma (18/27– 66.7%) and persistent wheeze (20/30–66.7%) were found to be atopic by the age of 2years.

Frequency of episodes of respiratory illnesses

In the first year of life, 73.5% had ≥3 episodes of ARI, the majority of these being URI (Table 2). 52.4% of children experienced ≥3 episodes of URI, 59.2% ≥1episode of febrile ARI and 66% ≥1 episode of LRI (Table 2). 26.5% had at least one episode of wheezy LRI and similar percentage (26.5%), at least one episode of febrile LRI.

Predictors for current asthma and persistent wheeze at 10years

Presence of eczema at 5years and 10years and ARC by 5years were significantly associated with current asthma at 10years (Table 3). These characteristics and biparental atopy were also found to be significant for persistent wheeze at 10years (Table 3).

Atopy at 2years, 5years and those with persistent atopy were found to have >2.5times the risk of current asthma at 10years (Table 3). This risk for current asthma increased substantially for children who had positive SPT at 10years (RR 17.14; 95%CI 2.39–122.83; p=0.005) (Table 3). Similar significant associations were also found for persistent wheeze at 10years, in particular if they were atopic at 10years (RR 3.30; 95%CI 1.34–8.11; p =0.009) (Table 3).

Children who wheezed in the first 3years of life (RR 3.79; 95%CI1.52–9.46; p=0.004), and those who wheezed throughout the 1st 5 years (RR 7.48; 95%CI3.73–15.00; p<0.001) were significantly more likely to have current asthma as well as persistent wheeze (Table 3).

No significant associations were found between URI and wheeze or asthma at 10years.

In contrast, children who had experienced HRV-associated wheezy LRI in year1 were more likely to have persistent wheeze at 10years (RR1.99; 95%CI1.04–3.84; p=0.04) (Table 3). There was a similar trend for current asthma, but this association failed to reach statistical significance.

Stronger associations were seen with early febrile LR1. Children who experienced ≥1 episode of febrile LRI in year1 had >2times the risk for current asthma (RR2.57; 95% CI1.33-4.98; p=0.005) and persistent wheeze (RR2.12; 95%CI1.14–3.95; p = 0.018) at 10years. This

relationship between febrile LRI and current asthma and persistent wheeze appeared strongest if they were associated with RSV (Table3).

Predictors for persistent wheeze and current asthma in relation to time of atopic sensitisation

Children who experienced any febrile respiratory infection had increased likelihood of current asthma (Table 4). This was however only seen in the group of children who were found to be sensitised by 2years of age. This association increased more than 2-fold for current asthma (RR4.92; 95%CI2.59-9.36; $p<0.001$) (Table 4) if the febrile infection involved the lower respiratory tract. There was also an increased association for febrile infections and persistent wheeze (RR 2.29; 95%CI1.20-4.40; $p<0.0012$) and similarly, this risk increased for febrile LRI (RR3.51; 95%CI 1.83–6.70; $p<0.001$) (Table 5),.In contrast, wheezy LRI in year1 were not significantly associated with current asthma or persistent wheeze at age 10years (Table 3). HRV-associated wheezy LRI were significantly associated with current asthma (Table 4) and persistent wheeze (Table 5) in those atopic after 2 years of age.

Discussion

In an earlier publication on the 5yr findings from this birth cohort of high risk children, we reported current wheeze and/or asthma at outcome age was significantly associated with either wheezy or febrile LRI during the first year of life[15]. Moreover, these associations were observed in relation to infections associated with both RSV and HRV, although the effects were strongest for HRV, consistent with what has been reported for the COAST cohort[11]. We additionally found the associations of these infections with asthma were strongest in the subset of children who developed atopic sensitisation before the age of 2years[15]. This suggested that interactions may occur between inflammatory pathways related to anti-viral and allergen specific immunity, which contribute towards the subsequent development of the asthma phenotype[5]. Children who experienced >1 episode of wheeze associated with LRI during their first year had the highest prevalence of wheeze-related outcomes at 5yrs. The findings reported here for the same cohort at 10yrs contain many similarities but also some significant differences.

The waning of the association between wheezing LRI during year1 and subsequent asthma-related phenotypes ascertained at 10yrs versus 5yrs is of particular interest. As noted above, early wheeze is generally invoked as the "gold standard" in relation to early identification of children at high risk of subsequent persistent asthma, and depending on the breadth and depth of the clinical and immunological assessments made within individual studies, this variable has been associated with very high prevalence of asthma in mid-childhood[12]. Indeed our data in

the present cohort show a similar picture (Table 3), but only if wheeze is considered in isolation. When early atopic sensitisation is taken into account, as for the 5yr outcomes[15], infection-associated risk at 10years is once again restricted to the early onset atopics. Moreover the infections that are associated with maximum asthma risk in this target group are those associated with fever as opposed to wheeze (Tables 3-5).

This finding echoes earlier reports from Martinez et al from the Tucson cohort[2], which indicated that much of the wheeze encountered during infancy is transient ("transient early wheeze") and may be a result of small airway size which resolves over time with normal lung growth. Due to the small calibre of their airways at baseline, these subjects have a tendency to wheeze in response to even relatively mild stimuli which cause only small degrees of airway narrowing[2] and in community studies it is difficult to distinguish these subjects from those wheezing as a result of more intense airway inflammation. We have argued previously on the basis of findings from multiple studies that severe airways inflammation during the early postnatal phase of rapid lung growth has potential to disturb underlying tissue differentiation programs responsible for establishing normal lung function, and further, that the sequelae of such disturbances can "track" over time and manifest in later life as abnormal respiratory functions associated with the asthma phenotype[5, 18].

Our current findings are consistent with the hypothesis that febrile responses at the time of infection spreading to the lower respiratory tract may constitute a more reliable marker of the type of LRI that is associated with asthma development, than wheeze. The consistent findings in our 5year and 10year outcome data that such events are much more common in children with early atopic sensitisation may be explicable on the basis of our recent findings on viral-induced acute asthma exacerbations resulting in hospitalisation. As noted in multiple earlier studies[5], this high asthma susceptibility phenotype is restricted almost exclusively to children sensitized to

perennial aeroallergens, and our recent studies[19] suggest the underlying mechanism is IgE-dependent and involves a Th2-associated inflammatory cascade in which FcER1α^{+} activated myeloid cells which are recruited into the virus-induced inflammatory response in the lower respiratory tract, play a central role. The prominence in these viral-induced responses of activated myeloid cells, which are a major source of IL-1 and IL-18, note in this context the recent GWAS identifying *IL1RL1/IL18R1* variants in association with asthma risk[20], provides a plausible explanation for the presence of fever symptoms.

Our present study is not the first to report an association between fever during respiratory infections in children and risk for subsequent asthma. A large random survey of 5-7 and 9-11year old German children participating in ISAAC Phase II found retrospectively collected parental reports of repeated episodes of fever and antibiotic treatment in early life were strongly associated with increased asthma prevalence and current wheeze at schoolage[17]. Similar positive associations were found for hay fever and eczema. Because the information about number of febrile episodes occurring in year1 and antibiotics taken in the first 3years was collected retrospectively, it may be that parents of symptomatic children were more likely to recall more severe respiratory infections, that is, those associated with fever or those requiring antibiotics. In our prospective study, we found that antibiotics per se were not risk factors for asthma or atopy at 5years[21]. In another study, 2-16yr old children attending an asthma clinic who used acetaminophen for fever in the preceding 12months had increased risk for severe asthma[22]. No information was available on the causes for fever. Additionally, ISAAC Phase III reported paracetamol use for fever in year1 was associated with asthma symptoms at 6-7years[23]. Similar associations were reported for rhinoconjunctivitis and eczema. The authors concluded paracetamol was a risk factor for development of these conditions. It is plausible that

the occurrence of fever, for which paracetamol has been used, is the underlying risk factor and the observed associations may be a result of confounding by indication.

It is also pertinent to note the association between early severe LRI and asthma at age 5yrs[15] and (as shown here) 10yrs is not restricted to HRV but also includes RSV, particularly febrile RSV (Table 3). This is consistent with findings on 11yr olds from the Tucson cohort[6], but is at variance with data from the COAST cohort[11]. However, a notable feature of the present study was physician assessment of study subjects and NPA collection at every reported incidence of respiratory infection regardless of assumed severity. This is in contrast to the COAST Study where nasal lavage for viral identification was carried out only when the child had a moderate to severe respiratory illness, as classified by a symptom score card[12].

Although the authors acknowledge the small size of this study population is a limitation of the study, we have collected comprehensive information about the nature of each ARI including viral etiology on all respiratory illnesses experienced by the children in their first year of life.

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Our findings suggest that our unbiased approach might uncover associations between host responses to infection exemplified by fever and subsequent asthma pathogenesis, and the approach merits further testing in other prospective cohort studies.

In summary, prospectively collected data from our birth cohort of children at high risk of developing atopy and asthma show severe LRI associated with fever>38˚C are major risk factors for current asthma at 10years of age, particularly in children who develop allergic sensitization to aeroallergens by 2years of age, indicating an underlying IgE-dependent process occurring within the lungs which may be related to that recently demonstrated in viral-associated asthma exacerbations[19]. These data suggest that fever should be objectively measured in cohort studies of asthma aetiology.

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Table 1 Characteristics of the cohort

Characteristic	Number (%)
Male	85 (57.8)
Number of older sibs	
0	76 (51.7)
1	41 (27.9)
≥2	30 (20.4)
Pet ownership	108 (73.5)
Childcare attendance in 1st year of life	
Nil	90 (61.2)
1st 6months of age	20 (13.6)
7-12months of age	37 (25.2)
Antenatal smoking	5 (3.4)
Environmental tobacco smoke exposure	19 (12.9)
Maternal History	
Asthma	97 (66.0)
Hay fever	132 (89.8)
Eczema	61 (41.5)
Atopy	121 (82.3)
Paternal History	
Asthma	62 (42.2)
Hay fever	93 (63.3)
Eczema	22 (15.0)
Atopy	122 (83.0)
Biparental atopy	101 (68.7)
Duration of breastfeeding	
0 - 6weeks	11 (7.5)
7 - 12weeks	16 (10.9)
13 - 20weeks	11 (7.5)
21 - 26weeks	7 (4.8)
> 26weeks	102 (69.4)
Atopic Conditions (at 10years)	

Allergic Rhinoconjunctivitis (ARC)	72 (49.0)
Eczema ever	77 (52.4)
Current eczema	38 (25.9)
Atopy	88 (59.9)
Doctor diagnosis of Asthma (ever)	53 (36.1)
Current asthma	27 (18.4)
Persistent wheeze	30 (20.4)

Table 2 Frequency of different types of ARI in 1st year of life

No of episodes	ARI	URI	Febrile ARI	LRI	Wheezy LRI	Febrile LRI
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
0	5 (3.4)	17 (11.6)	60 (40.8)	50 (34.0)	108 (73.5)	108 (73.5)
1	14 (9.5)	24 (16.3)	48 (32.7)	45 (30.6)	25 (17.0)	39 (26.5)
2	20 (13.6)	29 (19.7)	29 (19.7)	26 (17.7)	13 (8.8)	0
≥3	128 (73.5)	67 (52.4)	10 (6.8)	26 (17.7)	1 (0.7)	0

ARI = Acute respiratory illnesses; URI = Upper respiratory illnesses; LRI =– Lower respiratory illnesses

Table 3 Adjusted* risk ratios for various early predictors for current asthma and persistent wheeze at 10years

Characteristic	**Current asthma at 10yr** (N = 27)	**Persistent Wheeze at 10yr** (N
	Relative Risk (95% CI) p value	**Relative Risk (95% CI) p va**
Gender (male) (n = 85)	1.46 (0.70, 3.03) 0.311	1.09 (0.57, 2.10) 0.787
Pet ownership (1st 5yrs) (n = 80)	0.78 (0.39, 1.54) 0.470	1.10 (0.57, 2.09) 0.782
Antenatal Smoking (n = 5)	0	0.98 (0.16, 5.82) 0.982
Day care in 1st year (n = 42)	0.71 (0.31, 1.64) 0.429	1.25 (0.64, 2.44) 0.514
Paternal asthma (n = 41)	1.29 (0.63, 2.64) 0.481	1.11 (0.55, 2.22) 0.772
Paternal atopy (n = 122)	2.56 (0.65, 10.13) 0.180	2.87 (0.73, 11.27) 0.131
Maternal asthma (n = 74)	1.43 (0.72, 2.88) 0.309	1.48 (0.77, 2.85) 0.241
Maternal atopy (n= 121)	1.72 (0.56, 5.28) 0.344	1.93 (0.63, 5.90) 0.246
Biparental atopy (n = 101)	2.62 (0.96, 7.14) 0.060	**2.96 (1.10, 7.99) 0.032**
Eczema at 5yr (n = 49)	**2.15 (1.10, 4.22) 0.025**	1.53 (0.81, 2.89) 0.190
Eczema at 10yr (n = 38)	**3.59 (1.85, 6.96) <0.001**	**2.87 (1.55, 5.30) 0.001**
Allergic Rhinoconjunctivitis by 5yr (n = 59)	**3.54 (1.66, 7.55) 0.001**	**2.24 (1.17, 4.29) 0.015**
Atopy		
Atopic at 6mth (n = 31)	1.58 (0.76, 3.25) 0.219	1.60 (0.82, 3.14) 0.169
Atopic at 2yr (n = 63)	**2.67 (1.28, 5.54) 0.008**	**2.67 (1.34, 5.29) 0.005**
Atopic at 5yr (n = 56)	**3.04 (1.45, 6.34) 0.003**	**2.10 (1.11, 3.99) 0.023**
Early atopy (by 2yr, nil at 5yr) (n = 34)	0.95 (0.42, 2.16) 0.902	1.21 (0.59, 2.46) 0.602
Atopic only at 5yr (n=22)	1.62 (0.74, 3.56) 0.227	1.14 (0.49, 2.65) 0.767
Persistent atopy (atopic at 2 & 5yr) (n = 35)	**2.56 (1.33, 4.94) 0.005**	**2.13 (1.14, 3.98) 0.017**
Atopic at 10yr (n = 88)	**17.14 (2.39, 122.83) 0.005**	**3.30 (1.34, 8.11) 0.009**
Wheeze phenotype		
Wheeze ever 0-3yr (n = 79)	**3.79 (1.52, 9.46) 0.004**	1.72 (0.87, 3.42) 0.121
Wheeze 3-5yr (n = 55)	**7.36 (2.96, 18.32) <0.001**	**3.90 (1.93, 7.91) <0.001**
Persistent wheeze (n = 31)	**7.48 (3.73, 15.00) <0.001**	**3.74 (2.06, 6.79) <0.001**
ARI in 1st year		
Wheezy LRI at 1yr (n = 39)	1.17 (0.56, 2.44) 0.684	1.19 (0.60, 2.37) 0.626
Wheezy LRI + RSV (n = 10)	1.10 (0.30, 3.98) 0.889	1.52 (0.56, 4.16) 0.413
Wheezy LRI + HRV (n = 26)	1.63 (0.77, 3.45) 0.202	**1.99 (1.04, 3.84) 0.039**
Wheezy LRI with HRV or RSV (n = 30)	1.37 (0.64, 2.92) 0.423	1.67 (0.86, 3.27) 0.133
Febrile LRI at 1yr (n = 39)	**2.57 (1.33, 4.98) 0.005**	**2.12 (1.14, 3.95) 0.018**
Febrile LRI + RSV (n = 10)	**3.11 (1.50, 6.45) 0.002**	**2.74 (1.34, 5.60) 0.006**
Febrile LRI + HRV (n = 13)	1.79 (0.73, 4.39) 0.202	2.06 (0.95, 4.47) 0.067

Febrile LRI + HRV or RSV (n = 20)	**2.67 (1.36, 5.27) 0.004**	**2.31 (1.20, 4.46) 0.013**
Any Wheezy or febrile LRI at 1yr (n = 53)	1.42 (0.72, 2.80) 0.314	1.55 (0.82, 2.92) 0.174

*Adjusted for gender, breastfeeding, pet ownership, older siblings, second hand tobacco smoke exposure and daycare attendance

ARI = Acute respiratory illnesses; LRI = Lower respiratory illnesses; HRV = Human Rhinoviruses; RSV = Respiratory Syncytial virus

Table 4 Adjusted*risk ratios for infections and current asthma (N = 27) at 10yrs in relation to age of sensitisation

Characteristic	Atopic by 2years (N = 69)	Atopic after 2years (N= 22)
	Relative Risk (95% CI) p value	Relative Risk (95% CI) p value
Whole population regardless of ARI history	2.09 (0.99, 4.43) 0.055	1.52 (0.68, 3.40) 0.306
Infections in 1st year		
Any febrile infections	**2.28 (1.16, 4.46) 0.017**	1.91 (0.75, 4.85) 0.176
Any febrile URI	1.22 (0.54, 2.72) 0.633	2.01 (0.82, 4.92) 0.126
Any LRI with fever	**4.92 (2.59, 9.36) <0.001**	1.13 (0.19, 6.79) 0.895
Any LRI without fever	1.53 (0.77, 3.07) 0.227	1.96 (0.81, 4.71) 0.134
Any wheezy or febrile LRI	**2.92 (1.45, 5.88) 0.003**	0.61 (0.09, 3.97) 0.601
Any wheezy LRI	1.41 (0.60, 3.33) 0.429	1.50 (0.42, 5.30) 0.530
Any wheezy LRI with fever	2.30 (0.98, 5.43) 0.057	2.33 (0.41, 13.07) 0.338
Any wheezy LRI without fever	1.61 (0.70, 3.71) 0.266	1.12 (0.19, 6.55) 0.903
Any wheezy LRI associated with HRV or RSV	1.36 (0.54, 3.43) 0.519	2.24 (0.75, 6.64) 0.146
Any wheezy LRI associated with HRV	1.36 (0.54, 3.43) 0.519	**3.36 (1.13, 9.99) 0.029**
Any wheezy LRI associated with RSV	1.47 (0.25, 8.61) 0.668	0

*Adjusted for gender, breastfeeding, pet ownership, older siblings, second hand tobacco smoke exposure and daycare attendance

ARI = Acute respiratory illnesses; URI = Upper respiratory illnesses; LRI = Lower respiratory illnesses; HRV = Human Rhinoviruses; RSV = Respiratory Syncytial Virus

Table 5 Adjusted* risk ratios for infections and persistent wheeze (N= 30) at 10yrs in relation to age of sensitisation

Characteristic	Atopic by 2years (N= 69)	Atopic after 2years (N = 22)
	Relative Risk (95% CI) p value	Relative Risk (95% CI) p value
Whole population regardless of ARI history	**2.35 (1.13, 4.90) 0.022**	1.22 (0.52, 2.86) 0.652
Infections in 1st year		
Any febrile infections	**2.29 (1.20, 4.40) 0.012**	2.12 (0.83, 5.38) 0.115
Any febrile URI	1.11 (0.50, 2.49) 0.795	**2.58 (1.04, 6.43) 0.041**
Any LRI with fever	**3.51 (1.83, 6.70) <0.001**	1.13 (0.17, 7.63) 0.903
Any LRI without fever	**2.11 (1.11, 3.99) 0.022**	1.44 (0.52, 3.99) 0.481
Any wheezy or febrile LRI	**2.64 (1.39, 5.02) 0.003**	0.67 (0.10, 4.54) 0.685
Any wheezy LRI	1.60 (0.73, 3.47) 0.238	1.74 (0.46, 6.58) 0.412
Any wheezy LRI with fever	2.05 (0.88, 4.79) 0.096	2.31 (0.32, 16.73) 0.406
Any wheezy LRI without fever	1.81 (0.84, 3.86) 0.128	1.43 (0.24, 8.51) 0.696
Any wheezy LRI associated with HRV or RSV	2.03 (0.97, 4.27) 0.061	2.38 (0.70, 8.11) 0.166
Any wheezy LRI associated with HRV	2.03 (0.97, 4.27) 0.061	**3.46 (1.01, 11.82) 0.048**
Any wheezy LRI associated with RSV	2.80 (0.93, 8.46) 0.068	0

*Adjusted for gender, breastfeeding pet ownership, older siblings, second hand tobacco smoke exposure and daycare attendance

ARI = Acute respiratory illnesses; URI = Upper respiratory illnesses; LRI = Lower respiratory illnesses; HRV = Human Rhinoviruses; RSV = Respiratory Syncytial Virus