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Timing of infection and development of wheeze, eczema, and atopic sensitization during the first 2 yr of life: the KOALA Birth Cohort Study

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PEDIATRIC ALLERGY AND IMMUNOLOGY

Timing of infection and development of wheeze, eczema, and atopic sensitization during the first 2 yr of life: The KOALA Birth Cohort Study

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To investigate if infections in pregnancy and very early in life present a risk for wheezing, eczema, or atopic sensitization in later infancy. A total of 2319 children enrolled before birth in the KOALA Birth Cohort Study were followed during their first 2 yr of life using repeated questionnaires. Information was obtained on common colds, fever, and diarrhea with fever as well as on wheeze and eczema at ages 3 and 7 months and 1 and 2 yr, respectively. Blood samples were collected from 786 children at age 2 yr for specific immunoglobulin E analyses. Children with a common cold [adjusted odds ratio (aOR) 2.03 95% CI 1.21–3.41] or fever episode (aOR 1.81 95% CI 1.10–2.96) in the first 3 months of life had a higher risk of new onset wheeze in the second year of life compared to children who had not. For children with diarrhea with fever in the first 3 months of life, the aOR for new onset wheeze in the second year of life was 3.94 (95% CI 1.36–11.40) compared to children without diarrhea. Infections becoming clinically manifest during the first 3 months of life may be a general marker for a wheezy phenotype.

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Key words: wheeze; asthma; child; infection; cohort studies

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Early-life infections have been implicated in asthma development both as protective and as risk factor. Protective effects of repeated viral infection, defined as episodes of runny nose (1) or febrile upper respiratory tract infections (2), on the subsequent development of asthma or allergic sensitization have been reported. Orofecal pathogens have likewise been suggested to protect against asthma among adults (3, 4). On the other hand, several upper and lower respiratory tract pathogens, among which respiratory syncytial virus (RSV), influenza virus and parainfluenza virus have been associated with increased risk of developing wheezing and asthma. Recently, a strong association was found between rhinovirus infection and wheezing in infancy (5).

Timing of childhood infection might be essential for the development of asthma and atopy and might explain some of the inconsistency found in literature (1–5). For the protective effect of microbial load on the developing immune system, time windows have been suggested, and in particular the prenatal period seems to be of importance (6). On the other hand, during the same period lung growth takes place and harmful events in this period might lead to reduced lung function and eventually to asthma later in life.

We therefore studied if infections of the mother during pregnancy and of the child in the first year of life were associated with the risk of wheeze, eczema, and atopic sensitization in later infancy (up to age 2 yr) in a large

prospective birth cohort study (KOALA study). Exposure to infection in the first year of life was studied using age intervals of exposure (i.e., first 3 months of life, 3–7 months-old, and 7–12 months-old, respectively) to study timing of exposure-outcome relation in more detail.

Methods

Study population and data collection

The KOALA Birth Cohort Study is a prospective study targeting the population located in the middle and southern part of the Netherlands. A detailed description of the study has been published elsewhere (7). In brief, between October 2000 and November 2002 women in their 34th week of pregnancy, with conventional or alternative lifestyle, were enrolled in the study. Pregnant women with conventional lifestyle (n = 2343) were recruited from a prospective study on pregnancy-related pelvic girdle pain and pregnant women with alternative lifestyle (n = 491) were recruited through alternative channels, such as organic food shops, anthroposophic doctors and midwives, or Steiner schools (7).

Data on prenatal, perinatal, and early life exposures such as, maternal infections during pregnancy, infections of the child, housing conditions, and lifestyle factors as well as on atopic outcomes were collected through repeated questionnaires (34th week of pregnancy and when the child was 3, 7, 12, and 24 months-old). From January 2002 onwards, biosampling has been performed including the sampling of venous blood at age 24 months (n = 829) for total and specific immunoglobulin E (IgE) analyses.

Only children of parents who signed informed consent and who had completed the first questionnaire at 34 wk of pregnancy were included in the study. Children born prematurely (gestational age < 37 wk) and children with Down syndrome were excluded from the study. The KOALA Study was approved by the Ethics Committee of the University Hospital Maastricht.

Infections

Illness episodes indicating infections of the mother during the second and third trimester of pregnancy and of the child during the first 2 yr of life were assessed by questionnaires. In their 34th week of pregnancy, women were asked if they had had a common cold, fever episode (fever > 38°C), an influenza-like illness (fever > 38°C for several days, headache, muscle aches, and/or common cold), or diarrhea after the 3rd month of pregnancy. After the child was born, the parents were asked to fill out questionnaires when the child was 3, 7, 12, and 24 months-old, and each questionnaire included questions on fever episodes (excluding fever after vaccination), common cold, and diarrhea (loose or watery stools ≥ 5 times a day) with fever in the child. The questionnaires also addressed the presence of concurrent symptoms in other persons in the household as indication of infectious etiology.

Wheeze, eczema, and atopic sensitization

The parental questionnaire filled out at each follow-up included the ISAAC questions on wheeze and eczema (8). Parents were asked if the child had had 'wheezing or whistling' since the previous follow-up moment which could be answered by 'yes' or 'no'. 'New onset wheeze' was defined as wheeze reported for the first time in the respective period in life (i.e. between birth and 7 months-old, between 7 and 12 months-old, or between 12 and 24 months-old). 'New onset eczema' was determined by first positive parental response to the question if their child had an intermittent itchy rash in the past months. Children with only diaper rash, rash around the eyes and/or scalp scaling were not regarded as having developed eczema. Blood samples were analyzed for specific IgE against hen's eggs, cow's milk, peanuts, birch, grass pollen, cat, dog, and house dust mite using radioallergosorbent test (RAST) as described previously (9, 10). The detection limit for specific IgE was 0.13 IU/ml. Atopic sensitization was defined as the presence of at least one specific IgE level > 0.3 IU/ml at age 2 yr.

Statistical analysis

Missing data in the questionnaires were treated as missing in the analyses. Multivariable logistic regression analysis was used to fit the possible confounders into the model and to calculate the adjusted odds ratios (aOR) and corresponding 95% confidence intervals (95% CI). Possible confounders were identified from literature. Confounders included in the model were recruitment group (conventional; alternative), gender (male; female), parental history of asthma (no; 1 or both parents), maternal smoking during pregnancy (yes; no), number of older siblings (0; > 0), environmental tobacco smoke (ETS) exposure of the child [ETS exposure between birth and

7 months-old (yes; no); ETS exposure between 7 and 12 months-old (yes; no); ETS exposure between 12 and 24 months-old (yes; no)], duration of (exclusive and partial) breastfeeding (never; < 4 months; 4–6 months; > 6 months), maternal education [low (primary school, preparatory vocational or lower general secondary education); middle (vocational, higher general secondary or pre-university education); high (higher vocational or academic education)]. In addition, each model was adjusted for illness episodes indicating infections reported in the age interval in which the outcome was measured.

Results

Of the 2834 infants in the cohort at birth, 96 children were excluded because they had been born prematurely and another four children because of Down syndrome. After 2 yr of follow-up, 415 children had incomplete follow-up data, leaving 2319 (82%) children for analysis, 786 of whom had also provided a blood sample.

As Table 1 illustrates, the distribution of characteristics in children with complete follow-up at age 2 yr is comparable to the distribution in the whole cohort at birth. Recruitment period for blood sampling coincided with the period in which alternative participants were recruited and as a result the subgroup that provided blood samples included proportionally more families with alternative lifestyle. This is also reflected in the prevalence of certain characteristics associated with alternative lifestyle such as longer duration of breastfeeding, less ETS exposure, and higher maternal education level in this subgroup.

Eczema was present in 32.5% (754/2319) of the children in the first 2 yr of life; 17.2% of the children had eczema already during the first 6 months of life, 6.3% of the children had new onset eczema between 7 and 12 months of age, and 13.0% in the second year of life. For new onset wheeze between birth and age 7 months, between 7 and 12 months, and between 12 and 24 months, the proportions were 14.1%, 11.9%, and 7.1%, respectively. At the age of 2 yr, 27.4% (215/786) of the children were sensitized against one or more common allergens.

Most children (71.4%) had already had a cold in their first 3 months of life (Table 1). Fever episodes were less common in the first 3 months of life (15.1%). Only 2.0% of the children had diarrhea with fever during their first 3 months of life, in the second year of life this was almost 15%.

Illness episodes indicative for infections in the mother when pregnant were not associated with eczema, wheeze or atopic sensitization in the child (Tables 2–4). Common cold, fever episodes, and diarrhea with fever in the child were associated with new onset wheeze in the same time period as the infection-like symptoms occurred (Table 2). Infection-like symptoms experienced in the first 3 months of life remained a risk for new onset wheeze in later infancy, also when adjusted for infection-like symptoms occurring in the period in which new onset wheeze was measured (Table 2). Children with a common

Table 1. Characteristics of the KOALA Birth Cohort at birth and at 2-yr follow-up [n (%)]

	Birth	2-yr follow-up*	
	Questionnaire (n = 2734)	Questionnaire (n = 2319)	Blood sampling (n = 786)
Male	1388 (50.9)	1186 (51.2)	409 (52.0)
Female	1341 (49.0)	1132 (48.8)	377 (48.0)
Recruitment group			
Conventional	2259 (82.6)	1876 (80.9)	557 (70.9)
Alternative	475 (17.4)	443 (19.1)	229 (29.1)
Parental asthma			
No	2121 (82.5)	1881 (82.7)	657 (84.1)
1 or both parents	449 (17.5)	394 (17.3)	124 (15.9)
Siblings			
No older siblings	2173 (83.0)	1913 (83.1)	652 (83.0)
Older siblings	445 (17.0)	338 (16.9)	134 (17.0)
Breastfeeding (in months)			
Never	–	327 (14.6)	101 (13.1)
< 4	–	701 (31.3)	203 (26.3)
4–6	–	388 (17.3)	148 (19.2)
> 6	–	826 (36.8)	319 (41.3)
Maternal smoking during pregnancy			
No	2535 (92.7)	2176 (93.8)	748 (95.2)
Yes	199 (7.3)	143 (6.2)	38 (4.8)
ETS exposure child†			
ETS at age 3 or 7 months	–	1345 (58.6)	421 (53.8)
ETS at age 12 months	–	1097 (47.3)	337 (42.9)
ETS at age 24 months	–	1256 (54.2)	374 (47.6)
Maternal education			
Low	274 (10.2)	212 (9.2)	59 (7.6)
Middle	1128 (41.8)	945 (41.2)	291 (37.3)
High	1297 (48.1)	1135 (49.5)	430 (55.1)
Common cold			
Pregnancy	–	1480 (63.9)	544 (69.2)
Child's age 0–3 months	–	1599 (71.4)	541 (70.3)
Child's age 3–7 months	–	1963 (85.1)	667 (85.0)
Child's age 7–12 months	–	2030 (88.1)	692 (88.4)
Fever			
Pregnancy	–	213 (9.2)	86 (11.0)
Child's age 0–3 months	–	339 (15.1)	112 (14.5)
Child's age 3–7 months	–	1237 (53.5)	428 (54.7)
Child's age 7–12 months	–	1578 (68.5)	536 (68.9)
Diarrhea			
Pregnancy	–	514 (22.2)	165 (21.0)
Child's age 0–3 months	–	46 (2.0)	11 (1.4)
Child's age 3–7 months	–	203 (8.8)	46 (5.9)
Child's age 7–12 months	–	263 (11.5)	92 (11.8)

*Complete follow-up; questionnaires filled out at 7, 12, and 24 months.
†All categories combined (less than 1 h/wk, less than 1 h/day, between 1 and 4 h/day, more than 4 h/day).
ETS, environmental tobacco smoke.

Table 2. Risk for new onset wheeze in three periods during the first 2 yr of life in relation to timing of infection

	New onset wheeze					
	0–7 months		7–12 months		12–24 months	
	n/N	aOR (95% CI)*	n/N	aOR (95% CI)*	n/N	aOR (95% CI)*
Pregnancy						
Common cold	307/2190	1.30 (1.00–1.71)	224/1886	1.12 (0.83–1.53)	109/1571	0.98 (0.65–1.48)
Fever (> 38°C)	307/2189	0.77 (0.48–1.21)	224/1886	0.91 (0.56–1.47)	109/1568	0.88 (0.43–1.80)
Influenza-like illness	306/2188	1.17 (0.79–1.74)	223/1885	1.02 (0.64–1.63)	109/1569	0.80 (0.39–1.64)
Diarrhea	306/2187	1.11 (0.83–1.49)	224/1884	0.98 (0.69–1.38)	109/1569	0.72 (0.42–1.22)
Early life						
0–3 months						
Common cold	302/2137	1.56 (1.15–2.12)	217/1823	1.46 (1.03–2.06)	105/1517	2.03 (1.21–3.41)
Fever	299/2147	1.52 (1.11–2.08)	217/1836	1.22 (0.82–1.81)	106/1530	1.81 (1.10–2.96)
Diarrhea with fever	302/2146	1.81 (0.89–3.70)	217/1832	1.25 (0.45–3.44)	107/1525	3.94 (1.36–11.40)
3–7 months						
Common cold	309/2205	1.53 (1.04–2.25)	221/1877	1.55 (0.97–2.49)	108/1563	1.74 (0.89–3.43)
Fever	309/2211	2.10 (1.61–2.73)	223/1882	1.36 (1.01–1.83)	108/1568	1.00 (0.67–1.50)
Diarrhea with fever	308/2205	1.56 (1.07–2.27)	221/1878	1.82 (1.16–2.84)	109/1564	1.35 (0.68–2.68)
7–12 months						
Common cold			229/1908	2.42 (1.38–4.25)	109/1557	1.62 (0.77–3.43)
Fever			227/1912	3.75 (2.51–5.62)	109/1564	1.34 (0.85–2.11)
Diarrhea with fever			225/1899	2.56 (1.79–3.67)	108/1553	1.86 (1.06–3.24)

*Adjusted for recruitment group (conventional/alternative), gender (male/female), parental history of asthma (no/1 or both parents), maternal smoking during pregnancy (yes/no), environmental tobacco smoke (ETS) exposure of child for the respective age interval (i.e. (no/yes at age 3 months) (no/yes at age 7 months) (no/yes at age 12 months) or (no/yes at age 24 months), number of older siblings (0/> 0), duration of breastfeeding (never/< 4 months/4–6 months/> 6 months), maternal education (low/middle/high) and common cold, fever and diarrhea in the same age-interval as new onset wheeze.
aOR, adjusted odds ratio.

Table 3. Risk for new onset eczema in three periods during the first 2 yr of life in relation to timing of first infection

	New onset eczema					
	0–7 months		7–12 months		12–24 months	
	n/N	aOR (95% CI)*	n/N	aOR (95% CI)*	n/N	aOR (95% CI)*
Pregnancy						
Common cold	375/2198	0.93 (0.74–1.18)	112/1825	1.23 (0.80–1.87)	214/1610	0.97 (0.72–1.32)
Fever (> 38°C)	376/2197	0.94 (0.64–1.40)	112/1824	0.77 (0.38–1.58)	214/1608	0.84 (0.50–1.42)
Influenza-like illness	374/2196	0.83 (0.56–1.23)	111/1824	0.98 (0.52–1.84)	214/1610	0.81 (0.49–1.35)
Diarrhea	376/2195	1.06 (0.81–1.39)	111/1821	0.69 (0.41–1.16)	213/1609	1.12 (0.79–1.58)
Early life						
0–3 months						
Common cold	370/2145	1.22 (0.94–1.58)	107/1760	1.16 (0.74–1.82)	207/1554	1.18 (0.84–1.64)
Fever	370/2155	1.10 (0.81–1.51)	106/1770	1.46 (0.89–2.40)	208/1566	0.89 (0.58–1.37)
Diarrhea with fever	369/2154	0.61 (0.23–1.58)	107/1770	1.40 (0.41–4.77)	208/1563	0.75 (0.22–2.52)
3–7 months						
Common cold	380/2213	1.15 (0.83–1.59)	111/1820	0.89 (0.52–1.50)	214/1607	1.42 (0.90–2.24)
Fever	381/2219	1.11 (0.89–1.39)	112/1824	1.00 (0.67–1.49)	214/1610	1.32 (0.98–1.79)
Diarrhea with fever	381/2213	1.03 (0.70–1.51)	109/1819	1.12 (0.58–2.19)	214/1607	1.09 (0.65–1.84)
7–12 months						
Common cold			116/1846	1.68 (0.83–3.37)	213/1600	1.42 (0.84–2.39)
Fever			114/1847	1.09 (0.72–1.66)	214/1605	1.39 (0.99–1.94)
Diarrhea with fever			114/1840	1.77 (1.08–2.91)	212/1597	1.22 (0.78–1.90)

*Adjusted for recruitment group (conventional/alternative), gender (male/female), parental history of asthma (no/1 or both parents), maternal smoking during pregnancy (yes/no), environmental tobacco smoke (ETS) exposure of the child for the respective age interval (i.e. (no/yes at age 3 months) (no/yes at age 7 months) (no/yes at age 12 months) or (no/yes at age 24 months), number of older siblings (0/> 0), duration of breastfeeding (never/< 4 months/4–6 months/> 6 months), maternal education (low/middle/high) and common cold, fever and diarrhea in the same age-interval as new onset eczema.
aOR, adjusted odds ratio.

Table 4. Risk for allergic sensitization at age 2 yr in relation to timing of infection

	Allergic sensitization	
	n/N	aOR (95% CI)*
Pregnancy		
Common cold	210/775	1.21 (0.84–1.74)
Fever (> 38°C)	209/774	1.01 (0.60–1.68)
Diarrhea	210/775	0.94 (0.63–1.41)
Influenza-like illness	208/773	1.08 (0.66–1.76)
Early life		
0–3 months		
Common cold	207/759	0.79 (0.55–1.12)
Fever	207/763	1.19 (0.75–1.87)
Diarrhea with fever	208/762	0.32 (0.04–2.59)
3–7 months		
Common cold	210/774	0.74 (0.48–1.15)
Fever	210/772	1.20 (0.86–1.67)
Diarrhea with fever	209/772	0.99 (0.49–2.00)
7–12 months		
Common cold	209/772	0.92 (0.55–1.52)
Fever	208/767	0.95 (0.67–1.36)
Diarrhea with fever	207/767	1.12 (0.68–1.83)

*Adjusted for recruitment group (conventional/alternative), gender (male/female), parental history of asthma (no/1 or both parents), maternal smoking during pregnancy (yes/no), environmental tobacco smoke (ETS) exposure of the at age 24 months, number of older siblings (0/> 0), and duration of breast-feeding (never/< 4 months/4–6 months/> 6 months), maternal education (low/middle/high).
aOR, adjusted odds ratio.

cold or fever episode in the first 3 months of life had an about two times higher risk of new onset wheeze in the second year of life compared to children who had not had a common cold (aOR 2.03 95% CI 1.21–3.41) or fever episode (aOR 1.81 95% CI 1.10–2.96) in the first 3 months of life. For children who had had diarrhea with fever in their first 3 months of life, the risk for new onset wheeze in the second year of life was four times that of children without diarrhea (aOR 3.94 95% CI 1.36–11.40).

Infection-like symptoms after the first 3 months of life were also associated with new onset wheeze in later infancy; infection-like symptoms between 3 and 7 months of life were associated with new onset wheeze when the children were 7–12 months-old, but not thereafter.

For diarrhea with fever between 7 and 12 months of age, the risk for new onset wheeze in the second year of life was increased (aOR 1.86 95% CI 1.06–3.24), but for common cold and fever episodes experienced between 7 and 12 months-old no association with wheeze in the second year of life was seen. Eczema was not associated with childhood infections except for a modestly increased risk for new onset eczema in the second year of life in children with an episode of fever between 3 and 7 months-old or between 7 and 12 months-old (Table 3). Atopic sensitization at age two was not associated with any of the infection-like symptoms regardless of the age period in which they occurred (Table 4).

Discussion

In this prospective birth cohort study, an association was found between infection-like symptoms during the first 3 months of life and new-onset wheeze in later infancy. In particular, infants who had diarrhea with fever in the first 3 months of life had a substantially higher risk of new onset wheeze in the second year of life. No associations were seen between any of the infection-like symptoms experienced in the first 3 months of life and new onset eczema or allergic sensitization in the first 2 yr of life.

Infections in early life have been implicated in asthma development both as protective factor and as risk factor. Protective effects of (indices of) infection in early life on atopy and asthma have been found in school-aged children (1). Lower respiratory tract infections were found to be associated with increased risk of wheezing (1, 11), especially so in younger children (12). In the present study, we also found that infection-like symptoms were a risk factor for wheeze, but not for atopic sensitization or eczema. Fever in the first 3 months of life, as a general marker of infection, was associated with an almost two times higher risk of new onset wheeze in the second year of life. Others have found that febrile episodes between 7 and 12 months of age decreased the risk of the subsequent development of allergic sensitization or asthma with allergic sensitization at age 6 and 7 yr (2, 13). Upper respiratory tract infections in infancy, defined as episodes of runny nose, were also found to protect against asthma in 7-yr-old children (1). By contrast, very recently rhinovirus infection has been reported to be strongly associated with wheeze in young children (5). In line with the findings from the present study, rhinovirus infections have been found to increase the risk of wheeze at the age of 3 yr (5) and at 5 yr (14). Both previous studies (5, 14) investigated rhinovirus infections in the first year of life, whereas in the present study we found that common colds, most likely caused by rhinovirus infection, experienced as early as the first 3 months of life presented the greatest risk for new onset wheezing in the second year of life. For fever, as non-specific indicator of infection, and diarrhea with fever, as presumed indicator of gastrointestinal infections like rota- or norovirus, we found similar associations with wheeze when experienced in the first 3 months of life as we did with

common colds. These results suggest that infections that become clinically manifest very early in life may be a general marker for an infant wheezy phenotype, however, not necessarily resulting in asthma in later life. Immature innate immunity at birth, defined as the inability to mount appropriate γ-interferon (IFN-γ) responses to viral infection has been found to be associated with a higher risk of symptomatic viral infection in infancy (15) and may be especially important for severity of disease (15, 16). Moreover, in the Tucson Study, IFN-γ production at age 9 months was inversely associated with wheeze occurring before age 6 yr (17). Alternative mechanisms might involve prolonged non-specific airway hyper-responsiveness, as seen in atopics, resulting from an increased rate of symptomatic colds (18) or deficient interferon-β response, impaired apoptosis, and increased virus replication as demonstrated in bronchial epithelial cells from asthmatic subjects (19). We were surprised to find that diarrhea with fever, a symptom of gastro-intestinal infection, was the infection-like symptom most strongly associated with subsequent new onset wheeze. We observed that when for children diarrhea with fever was reported, in most cases (> 50%) for another house-hold member the same symptoms were reported in the same time-period, underlining the infectious nature of the symptoms (data not presented). The most common causes of gastroenteritis in children of this age are rotavirus and norovirus infection, and recently it was reported that rotavirus may also spread beyond the intestine to other sites, among which the lungs (20). In humans, shedding of this virus in the respiratory tract and pulmonary complications has been described (21–23). Although this finding might reflect a more general susceptibility to clinical infection coinciding with predisposition to wheeze, in analogy to the mechanism suggested for respiratory infections, it is tempting to speculate that rotavirus infection might also have impact on lung development in susceptible individuals. To our knowledge, no other studies have investigated gastro-intestinal infections and atopic outcomes in infancy, although studies have found that salmonellosis in infancy is associated with lower risk of asthma and atopy in later childhood or adolescence (24), and gastrointestinal infections have been associated with lower risk of asthma and allergies in young male adults (4). Although we found no protective effect of symptoms of gastro-intestinal infection in children up to age 2 yr-old, we cannot exclude the possibility that such an effect may become apparent when the children grow older.

Strengths of this study are its prospective, population based, design, and the large numbers of participants included, providing the opportunity to study new onset of symptoms at several ages in infancy. Because of the high follow-up rate after 2 yr, the study population during follow-up was comparable to the study population at time of inclusion for most population characteristics. The children providing blood samples for specific IgE analyses differed in some respects from the study population at time of inclusion because of the later start of blood sampling in the cohort. However, we do not expect our data to be systematically biased by differential response or differential loss to follow-up. A limitation of the present study is that we relied on parentally reported information on wheeze, eczema, and infections. Wheeze and eczema were measured using the ISAAC questions, which only have been validated for older children. Information bias is inherent to the use of questionnaires and we cannot exclude the possibility of information bias in the present study. When parents differ in the propensity to report infections and if those parents who tend to underreport infections also underreport atopic outcomes, spurious associations between infections and atopic manifestations may occur. A number of observations contradict this. First, this would be strongest for related symptoms such as respiratory infections and wheeze but this does not explain associations with dissimilar symptoms, such as diarrhea and wheeze. Second, if this was the case also eczema would have been overreported, but eczema was not associated with any of the infections studied. Also infection-like symptoms were assessed by questionnaire. In very young infants, a blocked nose is common and not necessarily of infectious nature (i.e. common cold). This may explain the high prevalence of common cold symptoms in the age group 0–3 month-olds in our study. However, common colds are most prevalent in the first year of life (mean annual number of episodes reported in a German birth Cohort study was 3.1 (s.d. 2.1) (25), and in an Australian study one-third of the infants was reported to have had an upper respiratory tract infection already by age 1 month-old (26). Several factors may have influenced the prevalence of infectious symptoms at the different ages, such as breastfeeding which has previously been found to protect against rotavirus seropositivity in the KOALA cohort (27). For the present study, we also found that breastfeeding protected against infectious symptoms whereas daycare attendance conveyed a risk. In the multivariable analyses, we adjusted

for these and other (potential) confounders and we therefore think it unlikely that these factors have largely influenced our results.

In conclusion, infection-like symptoms during the first 3 months of life are a risk factor for wheeze in later infancy but were not associated with eczema or atopic sensitization. As this was also found for infection-like symptoms other than those suggestive for respiratory tract infections, this suggests that infections that become clinically manifest during the first 3-months of life may be a general marker for a wheezy phenotype but are not necessarily causally related to the development of asthma later in life. On the other hand, the finding that diarrhea with fever was strongly associated with wheeze warrants further study concerning the association between enteric viruses and infant wheeze.

References

1. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ 2001: 322: 390–5.
2. Williams LK, Peterson EL, Ownby DR, Johnson CC. The relationship between early fever and allergic sensitization at age 6 to 7 years. J Allergy Clin Immunol 2004: 113: 291–6.
3. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. J Allergy Clin Immunol 2002: 110: 381–7.
4. Matricardi PM, Rosmini F, Riondino S, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. BMJ 2000: 320: 412–7.
5. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005: 116: 571–7.
6. Ege MJ, Bieli C, Frei R, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol 2006: 117: 817–23.
7. Kummeling I, Thijs C, Penders J, et al. Etiology of atopy in infancy: the KOALA Birth cohort Study. Pediatr Allergy Immunol 2005: 16: 679–84.
8. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995: 8: 483–91.
9. Aalberse RC, Koshte V, Clemens JG. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. J Allergy Clin Immunol 1981: 68: 356–64.
10. Schuurman J, Perdok GJ, Lourens TE, Parren PW, Chapman MD, Aalberse RC. Production of a mouse/human chimeric IgE monoclonal antibody to the house dust mite allergen Der p 2 and its use for the absolute quantification of allergen-specific IgE. J Allergy Clin Immunol 1997: 99: 545–50.
11. Nafstad P, Brunekreef B, Skrondal A, Nystad W. Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo Birth Cohort. Pediatrics 2005: 116: e255–62.
12. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF Jr. Effects of viral respiratory infections on lung development and childhood asthma. J Allergy Clin Immunol 2005: 115: 668–74.
13. Williams LK, Peterson EL, Pladevall M, Tunceli K, Ownby DR, Johnson CC. Timing and intensity of early fevers and the development of allergies and asthma. J Allergy Clin Immunol 2005: 116: 102–8.
14. Kusel MM, de Klerk NH, Kebadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol 2007: 119: 1105–10.
15. Copenhaver CC, Gern JE, Li Z, et al. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. Am J Respir Crit Care Med 2004: 170: 175–80.
16. Guerra S, Lohman IC, Halonen M, Martinez FD, Wright AL. Reduced interferon gamma production and soluble CD14 levels in early life predict recurrent wheezing by 1 year of age. Am J Respir Crit Care Med 2004: 169: 70–6.
17. Stern DA, Guerra S, Halonen M, Wright AL, Martinez FD. Low IFN-gamma production in the first year of life as a predictor of wheeze during childhood. J Allergy Clin Immunol 2007: 120: 835–41.
18. Xepapadaki P, Papadopoulos NG, Bossios A, Manoussakis E, Manousakas T, Saxoni-Papageorgiou P. Duration of postviral airway hyperresponsiveness in children with asthma: effect of atopy. J Allergy Clin Immunol 2005: 116: 299–304.
19. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005: 201: 937–47.
20. Blutt SE, Conner ME. Rotavirus: to the gut and beyond! Curr Opin Gastroenterol 2007;23:39–43.
21. Azevedo MS, Yuan L, Jeong KI, et al. Viremia and nasal and rectal shedding of rotavirus in gnotobiotic pigs inoculated with Wa human rotavirus. J Virol 2005: 79: 5428–36.
22. Wennergren G, Hansson S, Engstrom I, et al. Characteristics and prognosis of hospital-treated obstructive bronchitis in children aged less than two years. Acta Paediatr 1992: 81: 40–5.
23. Zheng BJ, Chang RX, Ma GZ, et al. Rotavirus infection of the oropharynx and respiratory tract in young children. J Med Virol 1991: 34: 29–37.
24. Pelosi U, Porcedda G, Tiddia F, et al. The inverse association of salmonellosis in infancy with allergic rhinoconjunctivitis and asthma at school-age: a longitudinal study. Allergy 2005: 60: 626–30.
25. Gruber C, Keil T, Kulig M, et al. History of respiratory infections in the first 12 yr among children from a birth cohort. Pediatr Allergy Immunol 2008: 19: 505–12.
26. Kemp A, Ponsonby A-L, Dwyer T, et al. The interaction between early life upper respiratory tract infection and birth during the pollen season on rye-sensitized hay fever and ryegrass sensitization – a birth cohort study. Pediatr Allergy Immunol 2009: 20: 536–44.
27. Reimerink J, Stelma F, Rockx B, et al. Early-life rotavirus and norovirus infections in relation to development of atopic manifestation in infants. Clin Exp Allergy 2009: 39: 254–60.