

Early childhood infections and immunisation and the development of allergic disease in particular asthma in a high-risk cohort: A prospective study of allergy-prone children from birth to six years

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The role of early childhood infections and immunisation in the development of allergic diseases remains controversial. To examine these associations, six hundred and twenty infants with first-degree relatives with allergic diseases were recruited into the Melbourne Atopy Cohort Study. Information on risk factors and outcomes was collected by interviewer administered questionnaire and was based on parental report and/or a physician's diagnosis. Risk factors examined included early childhood infections (including gastroenteritis, otitis media and lower respiratory tract infections) and immunisations in the first 2 yr of life. Outcomes were current asthma, allergic rhinitis and eczema at 6 yr of age. Univariate and multivariate regression analysis were used to estimate relative risk (RR) and assess confounding. By 6 yr, 79% of the original cohort remained in the study. Those with at least three episodes of gastroenteritis showed an increased risk (crude RR 2.36, 95%CI 1.41 3.95; adjusted RR 2.03 95%CI 1.50 2.75) for the later development of asthma at age 6. Of the scheduled immunisations, Sabin immunisation in the second year had a reduced risk of asthma at 6 yr (crude RR 0.60, 95%CI 0.37 0.98; adjusted RR 0.63 95%CI 0.39 1.02). Combined diphtheria and tetanus (CDT) immunisation in the first year had an increased risk of asthma at 6 yr (RR 1.76, 95%CI 1.11 2.78; adjusted RR 1.88 95%CI 1.28 2.77). Recurrent gastroenteritis in early childhood is associated with a later risk of asthma. This may reflect a cause and effect relationship, or exposure to common risk factors. In contrast, Sabin immunisation in the second year is associated with a decreased risk of asthma in later childhood. CDT immunisation in the first year may be a risk factor for asthma, but the need for CDT immunisation may also be a marker of increased risk of asthma in later childhood.

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Allergic diseases develop on a genetic background that is modulated by environmental factors, including exposure to early childhood infections (1). In 'developed' countries, allergic diseases are common, and the prevalence has increased over the past decades (1–3).

One proposed explanation is the hygiene hypothesis that states that an improvement in hygiene levels and decreased infection rates may affect the development of the immune system, creating a vulnerability to allergic diseases (4–6). Studies examining the association between childhood infections and the development of allergic disease (1, 7–9) have found conflicting results which may reflect variations in the type, site and timing of infection; the severity or level of exposure and the possibility of reverse causation (7, 8). A review of a large number of studies examining the association between infections and atopic dermatitis found that common early childhood viral infections including gastroenteritis either increased the risk of atopic dermatitis or were not associated; and bacterial and endoparasitic infections either decreased the risk of atopic dermatitis or were not associated (7).

In this context, the role of early childhood immunisation has been contentious. The findings from epidemiological studies examining immunisation and allergic disease have been inconsistent and varied for different vaccines and settings (10–17). It has been suggested that by preventing natural infection or by providing a different microbial exposure or altering the natural microbial flora, immunisation may contribute to the development of allergic diseases. However, it has also been suggested that by providing some microbial exposure, immunisation may conversely prevent the development of allergic disease.

In this article, we examine the associations between early childhood infections [including gastroenteritis, otitis media and lower respiratory tract infections (LRTI)] and then immunisations in the first 2 yr of life and the development of allergic disease in particular asthma in a cohort of children with a family history of allergic disease in first-degree relatives.

Methods

Study design

The Melbourne Atopy Cohort Study (MACS) is an ongoing prospective cohort study initiated in 1989, by enrolment of expectant mothers with at least one first-degree relative of the unborn baby having a history of asthma, allergic rhinitis, eczema or food allergies.

Data collection

The MACS recruited 620 infants born between February 1990 and November 1994, prior to birth by enrolling their expectant mothers. Previous publications have described the recruitment process in more detail (18).

Data were collected on potential risk factors including infections and immunisations, confounders and allergic outcomes, by telephone questionnaire administered by a trained allergy research nurse with the mothers. The initial interview with the expectant mothers collected information on allergic conditions, housing, marital status, smoking history and education. Subsequent interviews following the birth were conducted at 4-wk intervals until infants were 64-wk-old; then at 78 wk and at 2 yr; and then annually from the age of 2 until 6. Details were collected on the intervening period between interviews regarding symptoms of any illness and medications in the infant/child, including infections, immunisations and allergic diseases. This report presents an analysis of the data relating to early childhood infections and immunisations in the first 2 yr and allergic outcomes collected up until 6 yr of age.

Exposures

Infections. The information on each of gastroenteritis, otitis media and LRTIs including bronchitis, in the first 2 yr of life, was based on parental report of the child's symptoms and/or parental report of physician/doctor's diagnosis. With each telephone interview, the parent was questioned on the presence of specific symptoms for the period since the last telephone interview and whether they had attended a doctor and the diagnosis.

- (i) *Gastroenteritis* was recorded when symptoms of acute vomiting and diarrhoea were reported or diagnosed by a physician/doctor as reported by the mother
- (ii) *Otitis media* was recorded when fever and pulling at the ears were reported or diagnosed by a physician/doctor as reported by the mother
- (iii) *LRTIs including bronchitis* were recorded when fever, wheezing and cough were reported or diagnosed by a physician/doctor as reported by the mother.

Immunisations. Scheduled childhood immunisations in the first 2 yr of this cohort of children

(1992–96) included triple antigen [diphtheria, tetanus and pertussis (DTP)], combined diphtheria and tetanus (CDT), Sabin (oral polio vaccine) and measles mumps rubella (MMR). CDT immunisation was only recommended for those children with a history of a suspected adverse reaction to the pertussis component of DTP. BCG was (and is) not given as a routine to children in Australia. Pneumococcal, Meningococcal and hepatitis B immunisation were not routine scheduled immunisations at the time of the study. *Haemophilus influenzae* was first introduced midway through the study recruitment period; hence information was incomplete and was not collected (19). Immunisation information for the MACS cohort was collected only on those immunisations on the schedule at the commencement of the study: DTP, CDT, Sabin and MMR, but not on BCG, *H. influenzae*, Pneumococcal, Meningococcal and Hepatitis B immunisation. Information on immunisation was dichotomised as first and second year. For each immunisation, if at least one immunisation was received in that year, then immunisation was positive for the given year. Immunisation in the first year mutually excluded immunisation in the second year.

Outcomes

Allergic diseases at 6 yr including the preceding 12 months and were based on parental report of consistent symptoms and/or physician/doctor diagnosis (18):

- (i) *Asthma* was recorded if there had been any episode of wheezing illness diagnosed as asthma by a physician/doctor.
- (ii) *Allergic rhinitis* was recorded if there had been any nasal discharge and/or congestion in the absence of upper respiratory tract infection (URTI) that required treatment with an anti-histamine and/or nasal steroid and was attributed to allergic rhinitis by a parent or physician/doctor (18).
- (iii) *Eczema* was recorded if there had been a rash attributed to eczema by a parent or physician/doctor (18).

Confounders

Potential confounders considered were those likely to be related to both risk factors and outcomes and included: parental socio-demographics, allergic disease (i.e. asthma, eczema, allergic rhinitis, drug allergy or any food allergy);

parental smoking history; parental education; gender of child and older siblings. In addition, collected data on pet ownership of at least one dog and/or cat were also included as a confounder. Parental education level was defined as those undertaking any tertiary education or school only and was used as a proxy for socioeconomic status. For each childhood infection, the other infections and immunisations in the first 2 yr were confounders; and for each childhood immunisation, the other immunisations and infections in the first 2 yr were confounders. Early childhood atopic disease, skin prick test results for food allergens and reflux, had small numbers and were considered in sensitivity analyses.

Data analysis

The association between infections and immunisations in the first 2 yr and allergic disease outcomes at 6 yr was examined. Regression analysis using a linear model to the binomial family was used to calculate crude risk ratios and adjusted risk ratios. Results were expressed as relative risk or risk ratios (RR) with 95% confidence intervals (95%CI). STATA (release 9.2; Stata Corporation, College 129 Station, TX, USA, 2006) was used for all statistical analysis.

Results

Loss to follow-up

By 6 yr of age, 488 (79%) of the original birth cohort of 620 remained, representing a cumulative loss to follow-up of 21% (Fig. 1).

Parental characteristics

Parents of the MACS cohort were predominantly Australian or New Zealand born, married, tertiary educated and living in owner-occupied houses (Table 1). Most parents had never smoked, and the proportion of mothers who smoked was less than that of fathers. The most common self-reported allergic condition was allergic rhinitis, followed by asthma and then eczema. Allergic conditions and food allergies were more frequent in the mothers than the fathers.

MACS cohort characteristics

The MACS cohort was 51% male (318/620), and most had at least one older sibling at the time of



Fig. 1. Flow diagram of Melbourne Atopy Cohort Study data collection and follow-up numbers.

Table 1. Baseline characteristics of the parents of the Melbourne Atopy Cohort Study (MACS) cohort based on the pre-birth survey*

	Maternal		Paternal	
	n = 620	%	n = 615	%
Age (yr) mean (s.d.)†	31.2	(4.4)	33.4	(5.3)
Born in Australia or New Zealand	538	86.8	509†	82.5
Married	564	91.0	563	91.3
Education				
Completed 3° education	364	58.7	377‡	61.1
†Years education mean (s.d.)	13.4	(1.9)	13.5	(2.0)
Residence				
House	563	90.8	562§	91.7
Residence				
Owned property	508	81.9	506§	82.5
Social security	22	3.6	19§	3.1
Smoking				
Current	39	6.3	112	18.2
Never	461	74.4	409	66.5
Food allergies				
Milk	123¶	19.9	61	9.9
Egg	53¶	8.6	30	4.9
Other	190¶	30.7	94	15.3
Drug allergy	181¶	29.2	36	5.8
Allergic disease				
Any	512¶	82.7	375	61
Asthma	268¶	43.3	158	25.7
Allergic rhinitis	375¶	60.6	284	46.2
Eczema	241¶	38.9	126	20.5
Pet ownership**				
Dog	189	31.2		
Cat	171	28.3		

*MACS cohort recruited urban Melbourne.

†n = 618, ‡n = 617, §n = 613, ¶n = 619 **expressed per household, n = 605.

birth (371/620, 60%). Almost half had an allergic disease at 6 yr (226/486, 47%). The most commonly reported allergic disease for the MACS cohort was asthma (25%, 95%CI 22 30%), eczema (25%, 21 29%) and then allergic rhinitis (16%, 13 19%). At 6 yr of age, a combination of allergic diseases was not common: asthma and eczema (24/486, 5%), asthma and allergic rhinitis (21/486, 4%), all three allergic diseases (19/486, 4%) and then allergic rhinitis and eczema (9/486, 2%). MACS cohort lived in households with pet ownership of 31% for a dog and 28% for a cat (Table 1). Further details of the MACS cohort are described in a previously published study (28).

Early childhood infections

For the MACS cohort, over the first 2 yr, otitis media was reported by 59% (95%CI 55 63%), gastroenteritis by 38% (95%CI 34 42%) and LRTI including bronchitis by 19% (95%CI 16 23%). The frequency of each infection varied by age and showed a similar pattern, with low rates in the first 6 months, a steep increase over the second 6 months of life, and then a plateau or reduced rate of increase from about 12 months (Fig. 2).

Infection in the first 2 yr and allergic disease at 6 yr

Each of the three types of infection was associated with a modest increased risk of asthma. The average increased risk per infection episode ranged from 7% to 58% (otitis media RR 1.30, 95%CI 0.93 1.81; gastroenteritis RR 1.07, 95%CI 0.78 1.46 and LRTI including bronchitis RR 1.58, 95%CI 1.15 2.19).

In examining the frequency for each infection type in the first 2 yr, those with three or more episodes of gastrointestinal infection had an almost 2.5-fold increased risk of developing asthma (RR 2.36, 95%CI 1.41 3.95) (Table 2). A further sensitivity analysis of the association between gastroenteritis and asthma which excluded early childhood atopic disease, skin prick test results for food allergens and reflux gave robust consistent results. There was no association between any of the infection types and risk of eczema. There was an association between one episode of otitis media and allergic rhinitis.

The association between gastrointestinal infection and asthma was further examined in a multivariate analysis. Adjusted risk estimates were similar to the crude estimates: those with three or more episodes of gastrointestinal

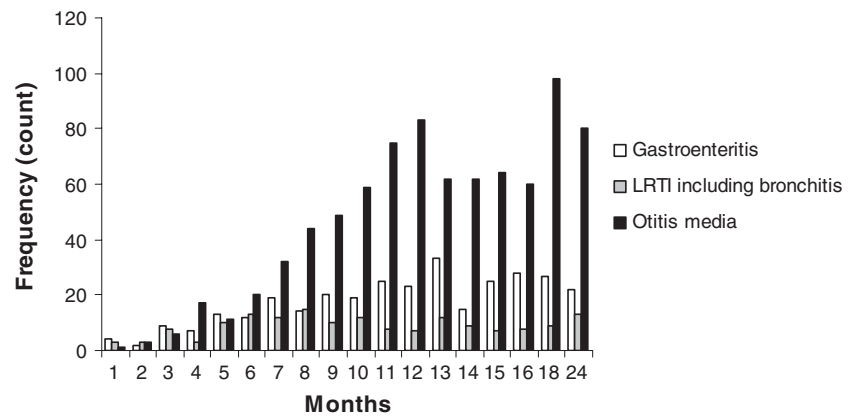


Fig. 2. Frequency of each infection for the first 2 yr.

infection had an almost twofold increased risk of developing asthma by 6 yr (RR 2.03 95%CI 1.50 2.75) (Table 3).

Immunisation status in the first 2 yr

For those immunisations scheduled for the first year, approximately 98% received at least one immunisation with DTP and 99% at least one immunisation with Sabin. Less than 5% received at least one CDT immunisation in each of the first or second years. For those immunisations scheduled for the second year, approximately 68% received DTP and 69% received MMR. Although Sabin immunisation was not scheduled for the second year, approximately 18% reported receiving Sabin immunisation in the second year (Table 4).

Immunisation status and allergic diseases

Sabin immunisation in the second year was associated with a decreased risk of asthma at 6 yr (RR 0.60, 95%CI 0.37 0.98). The only increased risk of allergic disease was seen for CDT in the first year and asthma at 6 yr (RR 1.76, 95%CI 1.11 2.78). Other scheduled immunisations administered in the first 2 yr were not associated with allergic diseases at the age of 6 (Table 2).

The association between Sabin and CDT immunisation and asthma was further examined in a multivariate analysis. Adjusted risk estimates were similar to the crude estimates: Sabin immunisation in the second year was associated with a decreased risk of asthma (RR 0.63 95%CI 0.39 1.02), and CDT immunisation in the first year was associated with an increased risk of asthma (RR 1.88 95%CI 1.28 2.77) (Table 3). MMR was also associated with a decreased risk in the multivariate analysis (Table 3).

Other risk factors

In the multivariate analysis, other factors that were associated with an increased risk of asthma included male gender, and those with at least one older sibling, mothers with a history of asthma, eczema and drug allergies, and fathers with a history of asthma and allergic rhinitis. Pet ownership was not associated.

Discussion

A key finding of this study was that all of the early childhood infections examined were associated with an increased risk of asthma at 6 yr, but the most consistent increased risk was with multiple episodes of gastroenteritis. Our finding that early childhood episodes of gastroenteritis increased the risk of asthma is novel and contrasts with previous studies that have found either no association (9) or a protective effect (20, 21). We found that the risk of asthma increased with the frequency of gastroenteritis in the first 2 yr and appeared to reach a threshold with three or more episodes. This finding is consistent with other studies that have suggested there may be an exposure dose effect with infection and the later development of allergic disease (7, 8, 20, 22). Most episodes of gastroenteritis were likely to have been viral, as rotavirus infection was the most common gastrointestinal infection in those under 2 yr during the study period (23). The association of otitis media and LRTI including bronchitis with asthma is consistent with earlier reports (1, 7, 8, 20). Overall, our findings were not consistent with the hygiene hypothesis, which states that early childhood infection would reduce the risk of later allergic disease.

The other key finding was that Sabin immunisation in the second year was associated with a consistent decreased risk of asthma at 6 yr. In

Table 2. Association between each infection type in the first 2 yr of life and immunisation status** at first or second years and each allergic disease at 6 yr for Melbourne Atopy Cohort Study cohort (n = 488)

	*Asthma	†Eczema‡	§Allergic rhinitis
	Crude risk ratio	Crude risk ratio	Crude risk ratio
Otitis media (OM)			
No URTI – OM (n = 182)	1.00	1.00	1.00
1 infection (n = 132)	1.17 (0.78 1.75)	1.23 (0.84 1.82)	1.75 (1.05 2.93)
2 infections (n = 74)	1.20 (0.74 1.93)	1.04 (0.63 1.71)	0.78 (0.35 1.75)
3 infections (n = 38)	1.35 (0.76 2.39)	1.55 (0.92 2.60)	1.74 (0.84 3.61)
4 infections (n = 27)	1.56 (0.85 2.84)	1.22 (0.61 2.43)	2.14 (1.01 4.53)
5 infections (n = 20)	1.87 (1.02 3.42)	1.13 (0.50 2.53)	0.83 (0.21 3.26)
6 or more infections (n = 10)	1.56 (0.72 3.35)	0.91 (0.32 2.58)	1.10 (0.29 4.25)
LRTI including bronchitis			
No LRTI – Bronchitis (n = 394)	1.00	1.00	1.00
1 infection (n = 71)	1.60 (1.12 2.29)	1.22 (0.82 1.82)	1.02 (0.56 1.84)
2 infections (n = 15)	1.46 (0.70 3.05)	1.10 (0.47 2.59)	0.88 (0.24 3.25)
3 or more infections (n = 9)	1.64 (0.66 4.09)	0.52 (0.08 3.25)	2.46 (0.98 6.21)
Gastrointestinal infection			
No gastroenteritis (n = 303)	1.00	1.00	1.00
1 infection (n = 139)	0.96 (0.67 1.37)	1.17 (0.85 1.63)	0.65 (0.38 1.12)
2 infections (n = 34)	1.07 (0.59 1.94)	0.62 (0.27 1.42)	1.43 (0.74 2.75)
3 or more infections (n = 12)	2.36 (1.41 3.95)	0.68 (0.19 2.45)	1.52 (0.55 4.17)
Triple antigen (DTP)			
1st year			
No (n = 6)	1.00	1.00	1.00
Yes (n = 482)	1.53 (0.25 9.22)	0.74 (0.24 2.33)	NC¶
2nd year			
No (n = 156)	1.00	1.00	1.00
Yes (n = 332)	0.74 (0.55 1.01)	1.16 (0.63 2.13)	0.96 (0.62 1.49)
CDT			
1st year			
No (n = 460)	1.00	1.00	1.00
Yes (n = 28)	1.76 (1.11 2.78)	1.16 (0.63 2.13)	1.41 (0.67 2.96)
2nd year			
No (n = 469)	1.00	1.00	1.00
Yes (n = 19)	1.04 (0.48 2.24)	0.20 (0.03 1.39)	1.74 (0.80 3.80)
Sabin			
1st year¶			
No (n = 1)	1.00	1.00	1.00
Yes (n = 487)	NC	NC	NC
2nd year			
No (n = 397)	1.00	1.00	1.00
Yes (n = 91)	0.60 (0.37 0.98)	1.32 (0.93 1.89)	1.07 (0.64 1.80)
MMR			
1st year¶			
No (n = 487)	1.00	1.00	1.00
Yes (n = 1)	NC	NC	NC
2nd year			
No (n = 351)	1.00	1.00	1.00
Yes (n = 137)	0.79 (0.58 1.09)	1.18 (0.90 1.54)	1.20 (0.84 1.71)

MMR, measles mumps rubella; LRTI, lower respiratory tract infection; DTP, diphtheria, tetanus and pertussis; CDT, combined diphtheria and tetanus.

*See Table 3 for multivariate analysis.

†See Table 3 for more multivariate analysis.

‡Eczema n = 486.

§Insufficient numbers for further multivariate analysis.

¶Insufficient numbers in comparison group to calculate estimate for first year.

**Scheduled immunisations for first year include DTP/CDT and Sabin.

Scheduled immunisations for second year include DTP/CDT, Sabin and MMR.

Bolded values show 95% CI that do not include value of 1.00.

addition, for the small number of children receiving CDT in the first year, there was an association with an increased risk of asthma. A similar pattern was not seen with CDT immuni-

sation in the second year. Most of the routine scheduled immunisations given at the recommended/scheduled times in the first 2 yr were not associated with an altered risk of allergic diseases

Table 3. Crude and adjusted risk ratio* for infection type in the first 2 yr, immunisation status at first or 2 yr and confounders and asthma at 6 yr for Melbourne Atopy Cohort Study cohort (n = 488)

	Crude risk ratio	Adjusted risk ratio
Otitis media (OM)		
No URTI – OM	1.00	1.00
1 infection	1.17 (0.78 1.75)	0.87 (0.60 1.26)
2 infections	1.20 (0.74 1.93)	1.05 (0.70 1.60)
3 infections	1.35 (0.76 2.39)	1.02 (0.63 1.63)
4 infections	1.56 (0.85 2.84)	1.03 (0.66 1.62)
5 infections	1.87 (1.02 3.42)	1.18 (0.70 2.01)
6 or more infections	1.56 (0.72 3.35)	1.05 (0.58 1.87)
LRTI including bronchitis		
No LRTI – Bronchitis	1.00	1.00
1 infection	1.60 (1.12 2.29)	1.36 (1.01 1.84)
2 infections	1.46 (0.70 3.05)	1.13 (0.57 2.25)
3 or more infections	1.64 (0.66 4.09)	2.48 (1.49 4.13)
Gastrointestinal infection		
No gastroenteritis	1.00	1.00
1 infection	0.96 (0.67 1.37)	1.05 (0.77 1.43)
2 infections	1.07 (0.59 1.94)	1.36 (0.94 1.97)
3 or more infections	2.36 (1.41 3.95)	2.03 (1.50 2.75)
Triple antigen (DTP)		
1st year	1.53 (0.25 9.22)	4.75 (0.88 25.58)
2nd year	0.74 (0.55 1.01)	0.74 (0.56 0.96)
Combined diphtheria and tetanus		
1st year	1.76 (1.11 2.78)	1.88 (1.28 2.77)
2nd year	1.04 (0.48 2.24)	1.00 (0.57 1.74)
Sabin		
1st year†	NC	NC
2nd year	0.60 (0.37 0.98)	0.63 (0.39 1.02)
Measles mumps rubella		
1st year†	NC	NC
2nd year	0.79 (0.58 1.09)	0.78 (0.61 1.00)
Socio-demographics child		
Gender (male)	1.53 (1.12 2.10)	1.61 (1.21 2.14)
Older siblings (at least 1)	1.22 (1.09 1.36)	1.27 (1.17 1.38)
Characteristics mother		
Education (tertiary)	1.01 (0.74 1.38)	0.94 (0.67 1.31)
Marital status (married)	1.02 (0.55 1.89)	0.75 (0.45 1.24)
Smoking (never)	0.82 (0.56 1.19)	0.70 (0.47 1.03)
Asthma	1.31 (0.96 1.77)	1.43 (1.07 1.90)
Eczema	1.12 (0.82 1.52)	1.32 (1.02 1.72)
Allergic rhinitis	0.94 (0.69 1.28)	0.87 (0.65 1.17)
Food allergy	1.04 (0.76 1.42)	1.14 (0.84 1.53)
Drug allergy	1.39 (1.02 1.90)	1.33 (1.02 1.74)
Characteristics father		
Education (tertiary)	1.04 (0.76 1.43)	1.11 (0.78 1.58)
Marital status (married)	0.95 (0.52 1.76)	NC
Smoking (never)	0.92 (0.66 1.28)	0.99 (0.71 1.40)
Asthma	1.29 (0.94 1.78)	1.34 (1.01 1.79)
Eczema	1.20 (0.84 1.71)	1.16 (0.84 1.61)
Allergic rhinitis	1.16 (0.86 1.57)	1.37 (1.04 1.81)
Food allergy	0.93 (0.63 1.37)	0.73 (0.50 1.08)
Drug allergy	0.78 (0.35 1.73)	0.89 (0.44 1.81)
Pet ownership		
Dog	0.79 (0.56 1.12)	0.84 (0.61 1.14)
Cat	1.04 (0.74 1.46)	1.05 (0.78 1.42)

LRTI, lower respiratory tract infection; DTP, diphtheria, tetanus and pertussis.

*Adjusted for all factors shown in Table 3.

Bolded values show 95% CI that do not include value of 1.00.

† Insufficient numbers in comparison group to calculate estimate for first year.

at 6 yr. The protective effect of Sabin immunisation in the second year and asthma at 6 yr was consistent with the findings for MMR (adjusted estimate) in the second year in this study and from another study of atopic disease (16). Other studies have not documented such an association (14, 15).

Biological plausibility

The observed increased risk of asthma at age 6 in relation to gastrointestinal infections before the age of 2 cannot be explained by direct local stimulation or irritation which has been suggested as one explanation for the increased risk with respiratory tract infections and asthma (24). Several studies have suggested that there may be different effects on the risk of allergic disease depending on the type of infection: viral infections may be associated with an increased risk of allergic disease or with no change in the risk; whereas bacterial and parasitic infections may be protective or show no association (1, 7). However, one study of parasitic gastrointestinal infections in later childhood and older age groups found an increase in IgE (25) usually associated with allergic disease.

Our findings are consistent with a proposed role for gastrointestinal (GIT) mucosal immunity in the development of allergic disease. It has been suggested that gut colonisation in early life may affect the subsequent differentiation of T-cell populations and alteration of the gut microflora may be a key mechanism in the development of allergic disease (7, 8, 26, 28). Frequent gastrointestinal infections in early childhood may alter the development of mucosal immunity or alternatively may be a marker of innate delayed/aberrant development of the immune response, associated with the development of allergic disease (28). We found that the risk of asthma increased with the frequency of gastroenteritis in the first 2 yr and appeared to have a threshold at three or more episodes. However from our study, it is difficult to discern whether the frequency and/or timing of gastrointestinal infection is crucial.

The protective effects of the orally administered Sabin vaccine in the second year may reflect an alteration in the development of the immune response including local GIT mucosal immunity, either by providing a different stimulus or by the prevention or modification of gastrointestinal infection. Such mechanisms would be consistent with our finding that early gastrointestinal infection in the first 2 yr increased the risk of asthma

Table 4. Number with at least one immunisation episode by vaccine in the first 2 yr of life for Melbourne Atopy Cohort Study cohort

	2nd year			2nd year			2nd year			2nd year	
	–	+		–	+		–	+		–	+
*DTP			*CDT			*Sabin			*MMR		
1st year											
–	9	5	–	573	17	–	8	1	–	205	412
+	219	387	+	24	6	+	506	105	+	2	1

MMR, measles mumps rubella; DTP, diphtheria, tetanus and pertussis; CDT, combined diphtheria and tetanus.

*Of the original 620 enrolled with at least one immunisation in that year for the given immunisation.

at 6 yr. Alternatively, Sabin administration in the second year may reflect factors related to delayed immunisation or critical timing such as being administered in the second year as the adjusted estimate for MMR (an immunisation usually administered in the second year) was associated with a decreased risk as well.

The finding that CDT immunisation in the first year was associated with an increased risk of asthma was consistent with the findings of Nakijima et al. for DTP (12) and provides support for the postulated role of the diphtheria component in the development of asthma by age 6 from epidemiological and laboratory studies (10, 13) as CDT does not contain pertussis. We did not find an increased risk of asthma with DTP, perhaps because of the high coverage and insufficient numbers in a comparison group.

The different findings for CDT immunisation in the first and then second years of childhood and asthma in later childhood may reflect the development of the immune response. The findings for CDT in the second year were consistent with several other studies that found no association between DTP and allergic disease (14, 15), or a small decreased risk (16, 17), but differed from those that found an increased risk of childhood asthma with DTP (11, 12). Therefore, the timing of immunisation may be important. It may be that the maturation of the immune response and the process of immune deviation influence whether an allergic tendency will develop upon exposure (28). The requirement for CDT following a reaction to DTP may be a marker for a group of children with delayed or altered development of their immune systems and consequent allergic tendency. Regardless, the requirement for CDT may be a useful marker to identify those with an increased risk of later allergic disease, especially for those without any history of early allergy.

Strengths and limitations

The main strengths of this study were its prospective design with reports of exposure to

early childhood infections and immunisations in the first 2 yr of life being collected prior to the outcome being the development of allergic diseases at 6 yr of age; as well as the quality of the follow-up including the frequency of assessment, retention and length. The follow-up rate of 79% for the MACS cohort at 6 yr was high, so it is unlikely that selective attrition bias could have influenced these findings. It was also reassuring that findings for confounders/other risk factors in the multivariate analysis were consistent with previous findings in the literature (5, 28, 29).

The calculated risk may overestimate the risk for the general population of children, as our findings are specific for a high-risk cohort with a strong family history of allergic disease in first-degree relatives. However, a comparison of our findings with those for 6–7-yr-olds from the Australian arm of the ISAAC study in which the participants were not selected for a family history of atopy found a similar prevalence of asthma (30). In contrast, the prevalence of eczema, allergic rhinitis and combinations of allergic diseases in our study was higher than the Australian ISAAC study (30). As suggested by the CDT results, it may be that the immune response in high-risk children develops or functions differently (28) predisposing to both adverse reactions to immunisations such as DTP and the development of allergic disease.

It is possible that additional confounders not included in the multivariate analysis may explain our findings. From the literature factors associated with allergic disease, in particular asthma may include perinatal risk factors and childcare. However, to be a confounder, they would need to be associated with both infection or immunisation and allergic disease. A potential limitation in examining additional confounders for this study may be insufficient power. Our study did not collect data on perinatal risk factors or childcare. However, in the future studies to collect information and examine additional confounders are planned including perinatal risk factors using data linkage.

The use of parental reporting may be less reliable than other ways of measuring the exposures and outcomes such as physician/doctor diagnosis (20). As such, parental or physician reporting may have resulted in misclassification. However, given the data were collected prospectively any potential misclassification is likely to be non-differential and result in a null outcome. Therefore, our positive findings are unlikely to be attributed to any non-differential misclassification. In addition, a study comparing the ISAAC definitions of allergic conditions used as a recognised 'gold standard' in large-scale epidemiological studies found good agreement with the definitions for allergic disease used in the MACS (A Lowe PhD Thesis awarded 2007/08).

The diagnosis of asthma was recorded if there had been any episode of wheezing illness diagnosed as asthma by a physician/doctor. It was not possible at that time to confirm the clinical diagnosis with lung function testing as at that time traditional spirometry was the only technique available, and it was not suitable for children <7 yr; and newer techniques such as forced oscillation were not widely available in the 1990s. As the diagnosis of a LRTI was based on wheeze and cough, there may have been misdiagnosis, making it more difficult to examine the relationship between LRTI and asthma and similarly for upper respiratory infections with otitis media and allergic rhinitis. However, the definition of gastroenteritis was distinct from that of the defined allergic disease outcomes including asthma.

Our study did not have microbiological confirmation of episodes of gastroenteritis as no faecal specimens were collected. However, as mentioned previously, most episodes of gastroenteritis were likely to have been viral, as rotavirus infection was the most common gastrointestinal infection in those under 2 during the study period (23).

Recall problems with parental reporting is unlikely with four weekly surveys in the first 2 yr and given the prospective design. Recall bias is more of an issue with retrospective studies. Detection bias with a tendency to over-report or to more frequently access clinical care for both early childhood infections and later for atopic diseases at 6 yr contributing to the associations observed is unlikely, as given the prospective design detection bias is unlikely to be differential.

Loss to follow-up is a potential issue for prospective studies as selective loss to follow-up may bias the results. It is not possible to test whether loss to follow-up has influenced the associations reported as information on out-

comes in those lost to follow-up is not available. However, it seems unlikely that selective attrition has had a major impact as the rate of follow-up was relatively high being almost 80% by 6 yr which is the strength of the study.

Conclusions

The findings of an increased risk of asthma with early childhood gastroenteritis and a decreased risk of asthma with Sabin immunisation are consistent with a possible key role for GIT mucosal immunity in the development of asthma. Further examination of these associations is important. Potential implications include a need for a higher level of clinical suspicion and monitoring for asthma amongst those children with recurrent gastroenteritis. As well, there are important implications for early childhood immunisation including orally administered immunisations such as Sabin and/or more recently introduced immunisations that prevent gastroenteritis such as the rotavirus vaccine in preventing the development of childhood asthma and other allergic diseases. In addition, the requirement for CDT immunisation in the first year may be a marker of increased risk of asthma in later childhood.

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