ORIGINAL ARTICLE

Age at childhood infections and risk of atopy

P Bager, T Westergaard, K Rostgaard, H Hjalgrim, M Melbye

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See end of article for authors' affiliations

Correspondence to: Dr M Melbye, Department of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark; mme@ssi.dk

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Background: It has been proposed that early age at exposure to common childhood infections is associated with a decreased risk of allergy. Previous studies on the possible association between allergy and infection with measles, mumps, rubella, and varicella have not been conclusive as most did not include information on exact age at exposure. The objective of our study was to investigate whether early age at exposure to these infections was associated with a decreased risk of atopy using information on exact age at infection.
Methods: The study population consisted of 889 pregnant women who participated in a national birth cohort study in Denmark and for whom detailed information on history of measles, rubella, varicella, and mumps before school entry (age 7 years) was available from school health records from Copenhagen. Atopic status was assessed serologically by a specific response to 11 common inhalant allergens using serum samples obtained from the women during pregnancy.
Results: Measles in the first year of life was associated with a higher risk of atopy than no measles before age 7 years (OR 3.36, 95% CI 1.47 to 7.68). There was no association between atopy and mumps, rubella, or varicella in the first 7 years of life or with measles acquired after the first year of life. The risk of atopy increased significantly with increasing number of childhood infections in the first 2 years of life (p_{trend}=0.01).
Conclusions: These findings do not support the suggestion that childhood exposure to measles, rubella, varicella, or mumps protects against atopy, even if acquired very early in life.

For the past three decades an increase in the prevalence of allergic rhinitis,[1–3] eczema,[1 3 4] and asthma[3 5] has been documented in developed countries. Similarly, evidence is accumulating of an increase in the prevalence of atopy as measured by skin prick testing and specific IgE.[6 7] These phenomena are not easily ascribed to genetic changes in populations[8 9] or to changed diagnostic criteria. Several theories based on environmental exposures as a consequence of changes in lifestyle have therefore emerged. In particular, consistent observations of an inverse association between family size and risk of atopy, allergic rhinitis, and eczema have led to the so-called "hygiene hypothesis".[10 11] This hypothesis suggests that the increase in allergy is explained by shifts in the pattern of infectious diseases in early life, affecting the maturation of the immune system. Thus, at birth the immune system is skewed towards a Th2 cytokine profile which is characteristic of allergic individuals,[12 13] but during infancy and early childhood this profile is normally shifted towards a non-allergic Th1 profile, perhaps through exposure to infections and other environmental stimuli.[12 14] It has been speculated that a delayed or absence of exposure to infections in childhood may cause the immune system to retain the Th2 profile, thus increasing the risk of allergy.[14]

Some epidemiological studies have suggested that exposure to measles and other common viral infections in childhood may protect against the development of allergy, but overall the results have been inconsistent.[15–23] However, epidemiological studies based on information on exact age at exposure to infections are lacking. We used a unique historical material of school health records representing a period prior to relevant vaccination programmes and with detailed information on dates of measles, rubella, varicella, and mumps to study whether exposure to these infections at an early age was associated with a decreased risk of atopy.

METHODS

Study population

The investigation was based on an ongoing nationwide cohort study of Danish pregnant women (The "Better health for mother and child" study). Women in this cohort who had completed their first interview during the period between 1 January 1998 and 16 December 1999 and who had lived in Copenhagen during their school years (age 7–16) were eligible for inclusion in the study. To identify these women the entire cohort (n=32 382) was linked with the civil registration system which contains present and historical information on residence using the unique personal identification number assigned to all Danish residents. A total of 1798 women who had lived in Copenhagen during their school years were identified. A manual search for the women's school health records was made in the archive for school health records for the Copenhagen municipality using information on date of birth, maiden and present names, as well as personal identification number when present. School health records were identified for 993 (55%) of the women. In general, school health records followed the pupil from school to school, so a woman's school health record was not expected to be in the archive if she ended up attending a primary school outside Copenhagen. Of the women with unidentified records, 77% did not live in Copenhagen at the end of their schooling (age 15 years).

Exposure data

The archive for school health records contains records of regular (mostly annual) health examinations of children who attended school in the municipality of Copenhagen between 1930 and 1990, as described elsewhere.[24 25] The records contain systematically recorded information on history of measles, rubella, varicella, and mumps obtained from parents by the school physician at school entry (age 6–7 years). Information on infection was recorded on more than 96% of the school health records. Time of infection was recorded either as the exact date (13%), the month and year (17%), the year (46%), or as yes before school entry (23%), and the precision of the recording did not vary by type of infection. Information on sibship size at school entry was also available on the records except for 49 women for whom the number of siblings was established through the civil registration system. Social class

Table 1 Risk of atopy* in a cohort of 889 pregnant women according to history of infection before the age of 7 years

Infection history	Cases/all (%)	OR (95% CI)	Adjusted OR† (95% CI)	p value
Measles				
No	48/205 (23.4%)	1 (reference)	1 (reference)	
Yes	207/672 (30.8%)	1.46 (1.01 to 2.09)	1.40 (0.97 to 2.03)	
Age (years)				
0	15/28 (53.6%)	3.77 (1.68 to 8.48)	3.36 (1.47 to 7.68)	0.01§
1	23/69 (33.3%)	1.64 (0.90 to 2.97)	1.56 (0.85 to 2.87)	
2–3	52/219 (23.7%)	1.02 (0.65 to 1.60)	0.97 (0.61 to 1.53)	
4–6	70/222 (31.5%)	1.51 (0.98 to 2.31)	1.45 (0.93 to 2.25)	
Unspecified‡	47/134 (35.1%)	1.77 (1.09 to 2.86)	1.74 (1.06 to 2.86)	
Missing	6/12 (50.0%)	–	–	
Rubella				
No	117/428 (27.3%)	1 (reference)	1 (reference)	
Yes	129/426 (30.3%)	1.15 (0.86 to 1.55)	1.13 (0.83 to 1.53)	
Age (years)				
0	19/46 (41.3%)	1.87 (1.00 to 3.49)	1.80 (0.95 to 3.42)	0.33§
1	12/45 (26.7%)	0.97 (0.48 to 1.93)	0.82 (0.40 to 1.67)	
2–3	28/99 (28.3%)	1.05 (0.64 to 1.70)	1.02 (0.61 to 1.68)	
4–6	36/120 (30.0%)	1.14 (0.73 to 1.78)	1.13 (0.72 to 1.78)	
Unspecified‡	34/116 (29.3%)	1.10 (0.70 to 1.73)	1.12 (0.71 to 1.79)	
Missing	15/35 (42.9%)	–	–	
Varicella				
No	74/268 (27.6%)	1 (reference)	1 (reference)	
Yes	181/606 (29.9%)	1.12 (0.81 to 1.54)	1.13 (0.81 to 1.58)	
Age (years)				
0	9/34 (26.5%)	0.94 (0.42 to 2.12)	0.95 (0.41 to 2.17)	0.64§
1	25/74 (33.8%)	1.34 (0.77 to 2.32)	1.32 (0.75 to 2.33)	
2–3	39/152 (25.7%)	0.90 (0.58 to 1.42)	0.93 (0.58 to 1.48)	
4–6	63/209 (30.1%)	1.13 (0.76 to 1.69)	1.13 (0.75 to 1.71)	
Unspecified‡	45/137 (32.8%)	1.28 (0.82 to 2.00)	1.30 (0.82 to 2.06)	
Missing	6/15 (40.0%)	–	–	
Mumps				
No	174/610 (28.5%)	1 (reference)	1 (reference)	
Yes	80/264 (30.3%)	1.09 (0.79 to 1.49)	1.08 (0.79 to 1.49)	
Age (years)				
0	1/5 (20.0%)	0.63 (0.07 to 5.64)	0.78 (0.08 to 7.15)	0.49§
1	2/13 (15.4%)	0.46 (0.10 to 2.08)	0.48 (0.10 to 2.22)	
2–3	25/81 (30.9%)	1.12 (0.68 to 1.85)	1.07 (0.64 to 1.77)	
4–6	32/100 (32.0%)	1.18 (0.75 to 1.86)	1.20 (0.76 to 1.91)	
Unspecified‡	20/65 (30.8%)	1.11 (0.64 to 1.94)	1.10 (0.62 to 1.93)	
Missing	7/15 (46.7%)	–	–	

OR=odds ratio; CI=confidence interval. *Atopy defined as a specific IgE level of ≥0.35 kU/l. †Adjusted for birth cohort, social class in childhood, and sibship size. ‡Positive history of infection before the age of 7 years but age at infection not specified. §p values are tests for homogeneity. These test for a differential effect of infection at different ages within the age span 0–6 years.

in childhood was derived from the father's occupation recorded on the health records at school entry.[26]

Blood samples

The women's atopic status was determined by serological analysis of serum samples obtained during pregnancy as part of the "Better health for mother and child" study. Serum samples were available from 889 (90%) of the 993 identified women and had been stored at –30°C. They were simultaneously analysed using a Phadiatop test (Pharmacia UniCAP) for specific IgE against a panel of 11 common inhalant allergens: horse, dog, cat, grass (*Phleum pratense*), herbs (*Artemisia vulgaris* and *Parietaria officinalis*), birch (*Betula verrucosa*), olive (*Olea europaea*), dust mites (*Dermatophagoides farinae* and *D pteronyssinus*), and mould fungus (*Cladosporium herbarum*). Women with specific IgE levels of ≥0.35 kU/l were classified as atopic.[27]

Statistical analyses

All risk ratios were calculated as odds ratios (OR) using logistic regression. The independent effect on risk of atopy of the specific infections occurring (a) at any age and (b) at specific ages before school entry (age 7 years) was assessed, with and without adjustment for potential confounding by birth cohort (≤1963, 1964–5, 1966–7, 1968–9, 1970–3, ≥1974), sibship size (1, 2, 3, 4+), and social class (I, II, III, IV, V, missing). Similarly, the effect on risk of atopy of the cumulative number of the four childhood infections acquired before the age of 1, 2, 3, and 4 years was assessed; p values were based on likelihood ratio tests and 95% confidence intervals (CI) were based on Wald's tests. Trends were estimated as the slope when the categorical variable of interest was treated as a continuous variable. The statistical software program SAS version 6.12 was used for the analyses.[28]

RESULTS

The women were aged between 17 and 44 years with a median of 30 years. Overall, 261 (29%) were classified as having atopy. Table 1 shows the risk of atopy according to age at infection with measles, rubella, varicella, and mumps.

A record of measles before the age of 7 years was associated with an increased risk of atopy (OR 1.46, 95% CI 1.01 to 2.09) compared with no measles before the age of 7. Adjusting for sibship size, birth cohort, and social class slightly reduced the estimate (OR 1.40, 95% CI 0.97 to 2.03). Among women who had measles before the age of 7 years, age at measles was significantly associated with the risk of atopy (p=0.01). Measles during the first year of life was associated with a 3.4-fold (95% CI 1.47 to 7.68) increase in the odds ratio of atopy compared with women without measles before the age of 7 years.

Table 2 Risk of atopy* in a cohort of 653† pregnant women by the cumulative number of the infections measles, rubella, varicella and mumps before the age of 1, 2, 3 and 4 years, respectively

Infection history	Cases/all (%)	Adjusted OR‡ (95% CI)
Sum of infections before age 1 year		
0	148/557 (26.6%)	1 (reference)
1	31/84 (36.9%)	1.62 (0.99 to 2.66)
2	6/11 (54.5%)	2.58 (0.80 to 8.31)§
3	0/1 (0%)	–
		p_{trend}=0.02
Sum of infections before age 2 years		
0	111/433 (25.6%)	1 (reference)
1	48/156 (30.8%)	1.35 (0.89 to 2.06)
2	24/54 (44.4%)	1.93 (1.11 to 3.38)§
3	2/10 (20.0%)	–
		p_{trend}=0.01
Sum of infections before age 3 years		
0	82/304 (27.0%)	1 (reference)
1	53/195 (27.2%)	1.04 (0.69 to 1.58)
2	42/118 (35.6%)	1.35 (0.87 to 2.10)§
3	8/34 (23.5%)	–
4	0/2 (0%)	–
		p_{trend}=0.21
Sum of infections before age 4 years		
0	54/210 (25.7%)	1 (reference)
1	58/192 (30.2%)	1.24 (0.79 to 1.94)
2	49/159 (30.8%)	1.27 (0.79 to 2.05)
3	21/76 (27.6%)	1.07 (0.60 to 1.91)¶
4	3/16 (18.8%)	–
		p_{trend}=0.60

OR=odds ratio; CI=confidence interval. *A total of 236 of the 889 women from the original cohort were excluded from the analyses due to incomplete information on history of all four infections or age at infection. †Atopy was defined as a specific IgE level of ≥0.35 kU/l. ‡Adjusted for birth cohort, social class in childhood, and sibship size. §Due to small numbers, categories of three or more infections were included in the category of two infections. ¶Due to small numbers the category of four infections was included in the category of three infections.

Overall, rubella infection before the age of 7 years did not affect the risk of atopy (table 1), although rubella during the first year of life was associated with an OR of 1.80 (95% CI 0.95 to 3.42) for atopy in comparison with women without rubella before the age of 7 years. There was no association between age at varicella or mumps and risk of atopy (table 1).

A total of 653 women had complete information on age at or history of all of the four studied infections. Among these women the risk of atopy increased with increasing number of infections before the age of 1 year (p_{trend}=0.02) and before the age of 2 years (p_{trend}=0.01), after which age no association was apparent (table 2). Exclusion of women with measles in the first year of life from the analyses did not change the direction of the observed correlation but the trends were no longer statistically significant.

DISCUSSION

Childhood infection with measles, rubella, varicella, or mumps, even if acquired very early in life, was not associated with a decreased risk of atopy as hypothesised. On the contrary, the risk of being atopic in adulthood increased in women who had measles during the first year of life.

Previous studies on the possible association between measles and atopy or allergic diseases later in life have provided conflicting results, with some authors suggesting an inverse association with measles in childhood,[16 18] some an association varying with age at exposure and type of outcome,[17 19] some no association,[15 20 21 23] and yet others a positive association.[22] Among these studies, an African study of 262 young adults originally reported an inverse association between the risk of atopy and having had measles in childhood,[16] while a more recent Finnish study encompassing over half a million subjects aged 1–19 years found a positive association between a history of measles and parent-reported allergic rhinitis, eczema, and asthma.[22] Four studies also investigated the possible association with varicella, mumps, or rubella infection and found either no association or an increased risk of atopy, hay fever, eczema, or asthma.[17 19–21] The only study that to some extent investigated the possible influence of age at exposure to the four infections on the risk of atopy was a nested case-control study of 282 subjects which found no association between atopy and having had the specific infections before or after the age of 1, 2, or 3 years.[19] The interpretation of most of these studies is, however, made difficult because of lack of information on the exact age at infection and also by factors such as vaccination to the studied infections, imprecise information on exposure and outcome, and recall bias.

The present study has to a large extent overcome the above mentioned limitations of previous studies. The exposure information came from detailed and systematically recorded data on specific age at infection. The distribution of measles according to age in our study was similar to seroprevalences reported just before the measles-mumps-rubella vaccination programme was introduced in Denmark in 1987.[29] All recorded infections were acquired before this vaccine was introduced. Furthermore, the information on childhood infections had been obtained prior to and independently of the blood samples. Atopy was measured objectively by serological testing, thereby avoiding the possible biases that accompany self- and parent-reported allergic disease. Although some parents did not report the exact date of infection, we find that this is unlikely to be related to atopy in adulthood and thereby to create bias.

We also investigated whether the risk of atopy was associated with the cumulative number of infections acquired at different ages in childhood. When measles, rubella, varicella, and mumps were combined in the analyses an increased risk of atopy associated with number of infections in the first 2 years of life was found. This finding is compatible with a study of 2111 subjects by Bodner *et al* who reported an increased risk of hay fever, eczema, and asthma with increasing exposure to rubella, varicella, and mumps in the first 3 years of life.[17]

Together these findings suggest that general characteristics of the occurrence of airborne viral systemic infections may modify the risk of atopy. Such properties could be age at exposure, dose of infection, duration and severity of disease, as well as the time interval between viral infection and allergen exposure. It has been suggested that large doses of antigen may induce Th2 cytokine responses[30] which, in turn, may increase the risk of allergic reactions, and that they may be particularly associated with exposure to infections early in life. It has also been reported that, immunologically, measles causes transient lymphopenia accompanied by increased levels of IL-4 which theoretically could promote allergic reactions by increased IgE isotype switching.[31–33] Interestingly, lymphopenia was found to be present for up to 2 months in infants after measles infection but for less than 1 month in older children.[32] This would be compatible with our observation of an increased risk of atopy with measles in infancy.

In conclusion, our findings do not support the suggestion that childhood infection with measles, rubella, varicella, or mumps protects against the development of atopy even if acquired very early in life. On the contrary, we observed an increased risk of atopy in women who had measles during the first year of life and with increasing number of the four studied infections during the first 2 years of life.

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Authors' affiliations
P Bager, T Westergaard, K Rostgaard, H Hjalgrim, M Melbye,
Department of Epidemiology Research, Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, Denmark

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