Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life

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Abstract

Objectives To determine whether early infectious diseases could explain the association between number of siblings and other markers of microbial exposure and the development of atopic dermatitis before the age of 18 months.

Design Cohort study. Information on atopic dermatitis, infectious diseases occurring before 6 months of age, number of siblings, early day care, pet keeping, farm residence, and background factors was collected in telephone interviews.

Setting Danish national birth cohort.

Participants 24 341 mother-child pairs.

Main outcome measures Incidence rate ratios of atopic dermatitis.

Results 13 070 children (54%) had at least one clinically apparent infectious disease before 6 months of age. At age 18 months, 2638 (10.8%) of the children had had atopic dermatitis. The risk of atopic dermatitis increased with each infectious disease before 6 months of age (incidence rate ratio 1.08, 95% confidence interval 1.04 to 1.13). The risk of atopic dermatitis decreased with each additional exposure to three or more siblings, day care, pet ownership, and farm residence (0.86, 0.81 to 0.93).

Conclusions Early infections do not seem to protect against allergic diseases. The protective effect of number of siblings, day care, pet ownership, and farm residence remained after adjustment for clinically apparent infectious diseases, suggesting that the effect is established independently early in life.

Introduction

Epidemiological studies have consistently shown an inverse relation between number of siblings and allergic diseases.[1] Strachan formulated the hygiene hypothesis, suggesting that the risk of allergic disease is reduced by infectious diseases in infancy transmitted by older siblings.[2] However, though factors associated with microbial exposure, such as early day care, pet keeping, and living on a farm, have likewise been associated with decreased risk of allergic diseases, the association between infectious diseases and allergic diseases has not been consistent.[3–12]

We investigated whether a protective effect of infectious diseases during the first 6 months of life could explain the association between number of siblings and other markers of microbial exposure and the development of atopic dermatitis before 18 months of age.

Methods

The study was based on mother-child pairs enrolled in the national birth cohort in Denmark, which comprised pregnant women consecutively recruited between 1997 to 2002.[13] Women were invited to take part in four computer assisted telephone interviews at 12 and 30 weeks' gestation (interviews 1 and 2) and when the child was 6 and 18 months old (interviews 3 and 4). Less than 2% of the women enrolled refused to take part. From April 2000 detailed questions about itchy rash and atopic dermatitis were integrated into the fourth interview. We included in our study all women who completed this modified fourth interview as well as the three previous interviews. By November 2002 (the start of our study), 44 779 women should have completed their interviews, but 20 438 had not done so. We enrolled the 24 341 remaining pairs. Data on day care and exclusive breast feeding were available for a subgroup of 15 430 mother-child pairs who had their third interview after April 2000.

Atopic dermatitis—In the fourth interview, the mothers were questioned about itchy rash and atopic dermatitis in their child. Validation of the questions is described elsewhere.[14] Cases of atopic dermatitis had to meet all three of the following criteria, as reported by the mother: itchy rash or atopic dermatitis diagnosed by a doctor; recurrent rash or rash in at least four consecutive half month periods; localisation of the rash in elbow and knee creases, on the hands, on the face, or in at least four places or generalised.[14]

Data on infectious diseases and use of antibiotics—In the third interview, the mothers were asked for details of any episodes of diarrhoea, colds, otitis media, pneumonia, or other infectious diseases. We obtained diagnoses and dates for admissions to hospital for infectious diseases from the national hospital discharge register.

Markers of microbial exposure—We obtained from the interviews data on number of siblings, pet keeping,

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farm residence, and, for the subgroup, day care before 6 months of age. We grouped number of siblings in to less than 3, or 3 or more.

Data on background factors—From the interviews we determined the date of birth and sex of the child and, for the subgroup, information on breast feeding. For parents, we determined the date of birth of the mother and details of allergic diseases (asthma, hay fever, atopic dermatitis), occupational class, educational level, smoking, cohabitation, and household income. Data on birth characteristics were obtained from the Danish medical birth registry.

Statistical methods—We used χ^2 tests to analyse the prevalence ratios for having had an infectious disease at 6 months of age according to characteristics of the child and its family. We used Cox proportional hazards models to examine the effect of infectious diseases on atopic dermatitis. When we analysed the data according to sex, we became aware of a significant interaction between sex, age, and atopic dermatitis: more boys than girls had atopic dermatitis in the first months of life, whereas this was not the case later. Subsequently we controlled for this in all analyses where results were different by time and sex. We presented the main associations separately for boys and girls.

Results

Overall 13 070 (54%) of 24 341 children had at least one clinically apparent infectious disease before 6 months of age, most of them (85%) having a cold. Boys had slightly more infectious diseases than girls (55% *v* 52%, $P < 0.001$).

A total of 2638 children had had atopic dermatitis by the age of 18 months; 1474 (56%) boys and 1164 (44%) girls. Overall, having had at least one infectious disease before 6 months of age was associated with atopic dermatitis (incidence rate ratio 1.09, 95% confidence interval 1.00 to 1.19). Table 1 gives details of the diseases reported in more than 250 children before 6 months of life. All tended to be associated with atopic dermatitis. The association increased in strength with number of infectious diseases (table 1). Adjustment for exclusive breast feeding for four months did not change the results (data not shown).

We explored the effects of markers of microbial exposure, previously associated with protection against allergic diseases, in a multivariable model with and without adjustment for infectious diseases (table 2). Farm residence, number of siblings, pet keeping, and early day care all tended to be inversely associated with risk of atopic dermatitis, with and without adjustment for infectious diseases. The overall incidence rate ratio of atopic dermatitis associated with having three or more siblings was 0.79 (0.62 to 1.01). In a separate analysis, we created a score of factors indicative of microbial exposures (having three or more siblings, farm residence, pet keeping, and early day care). After adjustment for number of infectious diseases, the number of factors was inversely associated with atopic dermatitis, the effect per factor being 0.86 (0.81 to 0.93) (table 2). In the same model, the additional effect for each infectious disease was 1.09 (1.03 to 1.14).

The effect of infectious diseases was stronger in girls than in boys (table 1). There was no sex difference in the effect of number of siblings, pet keeping, farm residence, or early day care (data not shown).

Discussion

Main findings

Infectious diseases in the first 6 months of life are associated with an increased risk of atopic dermatitis, while the opposite is true for several environmental factors indicative of microbial exposure. Our findings challenge the hypothesis that infectious diseases in infancy protect against the development of allergic disease.

Strengths and limitations

The strengths of our study include the large sample size and the population based cohort design. The diagnosis of atopic dermatitis was based on a set of diagnostic criteria, which we have found to be robust and reasonably specific.[14] The observed cumulative prevalence of 10.8% is lower than reported in other cohort studies of children of similar ages; this may be due to our strict diagnostic criteria. Importantly, we

Table 1 Adjusted incidence rate ratios (IRR) of atopic dermatitis (AD) according to type of early infection

	AD cases†	Person years†	IRR (95% CI) of AD associated with infection*		
			Both sexes	Boys‡	Girls‡
Type of infection§:					
Cold lasting ≥3 days	895/1743	12 429/21 634	1.07 (0.98 to 1.17)	0.98 (0.87 to 1.10)	1.19 (1.04 to 1.35)
Diarrhoea lasting ≥3 days	99/2539	1 055/33 004	1.38 (1.13 to 1.69)	1.18 (0.89 to 1.58)	1.63 (1.28 to 2.17)
Otitis media	95/2543	1 255/32 804	1.14 (0.92 to 1.40)	1.15 (0.88 to 1.50)	1.13 (0.82 to 1.57)
Pneumonia	54/2584	704/33 356	1.12 (0.85 to 1.46)	0.98 (0.69 to 1.40)	1.39 (0.91 to 2.13)
Chickenpox	47/2591	639/33 420	1.06 (0.79 to 1.42)	1.18 (0.80 to 1.73)	0.94 (0.60 to 1.46)
Exanthema subitum	33/2605	405/33 654	1.26 (0.89 to 1.78)	1.59 (1.03 to 2.45)	0.93 (0.53 to 1.65)
Admitted to hospital for infection	142/2496	1 771/32 290	1.11 (0.94 to 1.34)	1.04 (0.84 to 1.30)	1.23 (0.94 to 1.61)
Total No of infections:					
0	1571	19 321	1 (ref)	1 (ref)	1 (ref)
1	536	7 807	1.00 (0.90 to 1.10)	0.95 (0.83 to 1.09)	1.07 (0.92 to 1.24)
2	280	4 020	1.09 (0.96 to 1.25)	1.07 (0.90 to 1.28)	1.11 (0.91 to 1.36)
≥3	251	2 912	1.33 (1.16 to 1.53)	1.15 (0.95 to 1.40)	1.56 (1.28 to 1.91)
Increase per infection	—	—	1.08 (1.04 to 1.13)	1.04 (0.98 to 1.40)	1.13 (1.06 to 1.30)

*Adjusted for parental history of allergy, sex, number of siblings, season of birth, maternal age, and maternal education.
†Figures are exposed/not exposed, unless indicated otherwise.
‡Obtained in independent analyses. Adjusted for parental history of allergy, number of siblings, season of birth, maternal age, and maternal education.
§Data on specific infections presented for diseases reported by more than 250 children.

Table 2 Adjusted incidence rate ratios (IRR) of atopic dermatitis (AD) associated with factors indicative of microbial exposure.

Exposure	AD cases†	Person years†	IRR (95% CI) of AD*	
			Unadjusted	Adjusted for infections
No of siblings:				
0	1112	14 621	1 (ref)	1 (ref)
1	1096	13 339	1.06 (0.97 to 1.15)	1.03 (0.94 to 1.13)
2	364	4 973	0.96 (0.84 to 1.09)	0.94 (0.82 to 1.07)
3	59	939	0.88 (0.67 to 1.15)	0.86 (0.66 to 1.13)
4	7	188	0.53 (0.25 to 1.12)	0.53 (0.25 to 1.11)
Decrease per sibling	—	—	0.97 (0.92 to 1.03)	0.96 (0.91 to 1.02)
Farm residence	170/2668	2 584/31 476	0.95 (0.81 to 1.11)	0.90 (0.74 to 1.10)
Pet keeping	987/1651	14 600/19 460	0.87 (0.80 to 0.94)	0.87 (0.79 to 0.96)
Day care before 6 months†	181/1589	2 690/18 806	0.82 (0.70 to 0.96)	0.82 (0.70 to 0.96)
Total No of exposures‡:				
0	957	10 134	1 (ref)	1 (ref)
1	633	8 603	0.83 (0.75 to 0.92)	0.83 (0.75 to 0.92)
2	161	2 459	0.77 (0.65 to 0.91)	0.77 (0.65 to 0.91)
≥3	19	297	0.74 (0.47 to 1.17)	0.74 (0.47 to 1.17)
Decrease per exposure	—	—	0.86 (0.81 to 0.93)	0.86 (0.81 to 0.93)§

*Obtained in multivariable model including all variables at same time. Adjusted for parental history of allergy, sex, season of birth, maternal age, and maternal education.
†Figures are exposed/not exposed, unless indicated otherwise.
‡Subgroup analysis based on 15 430 children for whom information on day care was available.
§Boys: 0.85 (0.78 to 0.94), girls: 0.88 (0.79 to 0.97).

conducted the analyses as survival analyses including only infectious diseases occurring before the appearance of atopic dermatitis.

We looked at the effect of all reported early infectious diseases on the risk of an allergic disease while previous similar studies have looked at specific diseases only. In such studies, the presence of childhood diseases did not explain the protective effect of siblings on allergic diseases[4] and asthma,[6] though a protective effect of measles infection was observed. Seropositivity to hepatitis A virus, *Helicobacter pylori*, and *Toxoplasma gondii* seemed to explain the sibling effect to some extent in one study[10] but not in another.[5] In other studies, infectious diseases in neonates, infants or children did not explain the protective effect of siblings on hayfever, atopy, rhinitis, asthma, or allergic disease diagnosed by a doctor.[7–9 11 12]

Possible explanations

The tendency for reduced risk associated with number of siblings, early day care, pet keeping, and farm residence could reflect immune stimulation by environmental micro-organisms, which does not result in clinically apparent disease. Such stimulation may take place in the gut, where the permanent and enormous load of microbes ensures a constant source of stimulation.[15–18]

We measured clinically apparent infections and not merely exposure to microbes. Other studies have suggested that observed association between clinically apparent infectious diseases and atopic dermatitis may be caused by a defect in cellular immunity. In our study, the defect could be due to an immature immune system.[19 20]

Conclusions

In conclusion, we found that infectious diseases occurring early in life were associated with an increased risk of atopic dermatitis before 18 months. This contrasts with the previously held belief of a protective effect of early infections on the development of allergic diseases. The inverse association between atopic dermatitis and number of siblings, early day care, pet keeping, and farm residence remained after we controlled for number of clinically apparent infectious diseases, suggesting that these effects are mediated early in life and independently of clinically apparent infectious diseases.

What is already known on this topic

The risk of atopic diseases decreases with exposure to siblings, early day care, living on a farm, and pet keeping

Infectious diseases early in life may protect against the development of atopic diseases

What this study adds

Clinically apparent infectious diseases do not protect against the development of atopic diseases

The protective effect of siblings, as well as that of early day care, living on a farm, and pet keeping, is mediated independently of clinically apparent infections in the first 6 months of life

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Commentary: the defence of dirt

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As the Duchess of Windsor once remarked, one can never be too thin or too rich—wisely, she did not add too clean. The hygiene hypothesis aims to explain why some people have allergies and some do not, and why the prevalence of allergic disorders has been increasing over the past century. It suggests that the modern obsession with cleanliness may be counterproductive; in childhood, at least, it may encourage the development of allergic disorders. Benn and colleagues have attempted to untangle the link between infections in infancy and atopic disease.[1]

Formalised in the late 1980s, the hypothesis seemed to fly in the face of common sense. After all, hadn't the hygiene movement ushered in a dramatic reduction in infectious disease? This initial scepticism was compounded by the suspicion that infections might actually provoke allergy. Despite these doubts, the evidence kept piling up.[2] In epidemiological studies, factors such as large household size, a poor standard of living, not using antibiotics, and early exposure to farm animals all emerged as protective.

The original attempt to explain the immunological basis of the hygiene hypothesis invoked a loss of balance between two sets of the body's immune cells—the Th1 and Th2 lymphocytes.[3] A reduced exposure to childhood infection, it was argued, meant a low level of Th1 activity in the body, so bringing about a relative excess of Th2 activity—and a consequent tendency to allergy. This neat explanation began to fall apart when it was appreciated that Th1 mediated conditions, such as type 1 diabetes and inflammatory bowel disease, were also on the increase, and in the same regions of the world.

Clearly, any reinterpretation of the hygiene hypothesis had to take account of this parallel increase in conditions associated with Th1 and Th2. A recent attempt manages to do just this.[4] It suggests that the effect of hygiene is to diminish the body's production of a third group of players in the immune drama—the regulatory T cells. It is a shortage of these that results in the emergence of allergy. The driving force in this case, goes the argument, is our freedom not from pathogenic microbes but from a group of organisms including mycobacteria, lactobacilli, and helminth worms. These "old friends," as Rook describes them,[4] have lived with us for countless generations. In adapting to their more or less benign presence, the immune system has learned not to over-react. It exercises this self suppression by generating regulatory T cells.

In the absence of its "old friends" the system produces fewer of these cells. The consequence is a state of relatively uncontrolled effector T cell exuberance and, depending presumably on genetic factors of some kind, a predisposition to allergy or to more serious autoimmune conditions such as inflammatory bowel disease and diabetes. The findings reported by Benn and colleagues,[1] which refer only to "clinically apparent" infections, are entirely consistent with this view of the "old friends" being the organisms responsible for the protection against allergy.

Does this version of the hygiene hypothesis suggest a method of vaccination against allergy based on stimulating the body's production of regulatory T cells? It does, and preliminary experiments are already under way.[5] Immunology's love affair with dirt is blossoming and may yet bear fruit.

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