

Does previous infection protect against atopic eczema and recurrent wheeze in infancy?

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Summary

Background Frequent infection in infancy and early childhood has been hypothesized to explain the low prevalence of asthma and other atopic disease among children in developing countries (the so-called 'hygiene hypothesis'), but the low prevalence in Eastern Europe remains unexplained.

Objective To test the hygiene hypothesis in the Republic of Belarus by examining the relationship between gastrointestinal (GI) and respiratory infection and two potentially atopic outcomes in the first 12 months of life: atopic eczema and recurrent wheeze.

Methods We carried out two case-control studies nested within a large ($n = 17046$) randomized trial in Belarus, with cases defined as (1) first occurrence of atopic eczema ($n = 819$) and (2) second episode of wheezing ($n = 112$). Incidence density sampling was used to select four matched controls born within 1 month at the same hospital as the case. Exposure was defined as one or more episodes of GI or respiratory infection (examined separately) with onset > 7 days before onset of the case's atopic outcome. Analyses controlled for family atopic history, duration of exclusive breastfeeding, sex, birth weight, maternal education, and (for recurrent wheeze) maternal smoking.

Results For atopic eczema, prior GI infection occurred in 7.4% of cases vs. 6.0% of controls [adjusted OR = 1.27 (0.94–1.72)] and prior respiratory infection in 35.2% vs. 32.6% [adjusted OR = 1.14 (95% CI = 0.94–1.37)]. For recurrent wheeze, prior GI infection occurred in 9.8% of cases vs. 7.4% of controls [adjusted OR = 1.30 (0.60–2.82)].

Conclusion Our results do not support the hypothesis that infection protects against atopic eczema or recurrent wheezing in the first 12 months of life.

Keywords asthma, atopy, infection, wheezing

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Introduction

Eastern Europe has been reported to have a low prevalence of asthma and other atopic disease in children [1, 2]. Frequent infection and/or exposure to bacterial endotoxin during infancy have been associated with a low risk of asthma and atopy, and these associations have given rise to the so-called 'hygiene hypothesis' [3–7]. This has led to the notion that early infection may 'program' T-helper (Th) lymphocytes into the Th1 (vs. Th2) pathway, thereby lowering the risk of atopic disease [8–11].

Yet Eastern Europe is characterized by a low birth rate, small families, and infrequent use of day care. To our knowledge, frequent infection is undocumented in this region, and thus the low prevalence of atopic disease in the region may well have other explanations. We recently carried out a

large, cluster-randomized trial of a breastfeeding promotion intervention in the Republic of Belarus [12], an Eastern European country that was formerly part of the Soviet Union. Because of frequent and detailed follow-up with respect to both gastrointestinal (GI) and respiratory infection (the major outcomes for the trial), as well as atopic eczema and recurrent wheeze, our data enabled us to analyse the association between infection and these potentially atopic manifestations during the first 12 months of life.

Methods

We carried out two case-control studies nested within the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial of a breastfeeding promotion intervention modelled on the WHO/UNICEF Baby-Friendly Hospital Initiative [12]. A total of 17046 breastfeeding mothers and their healthy, full-term breastfed infants were enrolled from June 1996 to December 1997 in 31 randomized

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maternity hospitals during their postpartum stay. They were followed up at 1, 2, 3, 6, 9, and 12 months at an affiliated polyclinic (outpatient clinic for routine and illness care), with a 96.7% follow-up at 12 months. Detailed data were collected at each visit on GI and respiratory infection and on atopic eczema and wheezing.

The two case-control studies were based on two different atopic outcomes defined as cases: (1) first occurrence of atopic eczema and (2) recurrent (≥ 2 episodes) wheeze. Atopic eczema was defined as an itchy rash with a distribution on the face and/or extensor surfaces of the arms and/or extensor surfaces of the legs, and lasting at least 2 weeks or recurring after clearing for at least 1 week. Recurrent wheeze was defined as the second episode of respiratory infection associated with wheeze, as recorded by the examining polyclinic paediatrician. Four controls were selected per case using incidence density sampling; these controls were matched by maternity hospital at birth and birth date (± 1 month).

To ensure temporal precedence of exposure, the latter was defined as one or more episodes of GI or respiratory infection (each type of infection examined separately) with onset > 7 days prior to onset of the case's atopic outcome; the matched control was considered exposed if the onset of infection occurred at an age > 7 days younger than the age of the matched case at the onset of the case's outcome. Only prior GI infection was studied for recurrent wheeze, since, by definition, all cases of recurrent wheeze had prior respiratory infection. The diagnosis of GI infection was based on the algorithm of Rubin et al. [13] modified to ensure a minimum duration of 2 days: at least two symptoms among increased stool frequency, loose stools, vomiting, and documented temperature $> 38.5^\circ\text{C}$. Respiratory infection was defined as an upper respiratory infection (based on at least two symptoms among runny nose, cough, fast breathing, and docu-

mented temperature $> 38.5^\circ\text{C}$ [13]), or wheeze, croup, otitis media, or pneumonia diagnosed by the polyclinic paediatrician. Each of these diagnoses required a minimum duration of 2 days. The sample size for these studies was fixed by the design of the PROBIT trial and the incidence of the two case-defining outcomes in the overall cohort.

Statistical methods include 2×2 tables [crude matched odds ratios (ORs) and 95% confounding intervals (CIs)] and conditional logistic regression (adjusted ORs and 95% CIs) to account for the matching and to adjust for family history of atopy (presence or absence of history of asthma, hayfever, atopic eczema in the mother, father, or a sibling), duration of exclusive breastfeeding (< 3 vs. ≥ 3 months), sex, birth weight (2500–2999, 3000–3499, ≥ 3500 g), maternal education (primary, secondary, postsecondary, university), number of siblings in the household (0, 1, ≥ 2), and (for recurrent wheeze only) maternal smoking (yes or no) during pregnancy. SAS software (version 8.2) was used for all statistical analyses.

Results

Table 1 presents a baseline comparison of the cases and controls for both case-control studies. In both studies, cases and controls were similar with respect to maternal age, education, and smoking during pregnancy and infant gestational age and 5-min Apgar score. Both case groups showed a highly significant (vs. controls) male predominance. Atopic eczema cases were significantly more likely to have a positive atopic family history than their matched controls, and they had slightly but significantly higher birth weights. Recurrent wheeze cases were significantly more likely to have other children living in the household.

Table 1. Baseline comparison of cases and controls in both case-control studies*

Variable	Atopic eczema			Recurrent wheeze		
	Cases (<i>n</i> = 819)	Controls (<i>n</i> = 3276)	<i>P</i> -value	Cases (<i>n</i> = 112)	Controls (<i>n</i> = 448)	<i>P</i> -value
Maternal age (years)			0.311			0.797
< 20	122 (14.9%)	489 (14.9%)		18 (16.1%)	66 (14.7%)	
20–34	653 (79.7%)	2651 (80.9%)		86 (76.8%)	356 (79.5%)	
≥ 35	44 (5.4%)	136 (4.2%)		8 (7.1%)	26 (5.8%)	
Maternal education			0.906			0.184
Incomplete secondary	39 (4.8%)	141 (4.3%)		6 (5.4%)	11 (2.5%)	
Complete secondary	258 (31.6%)	1013 (30.9%)		32 (28.6%)	151 (33.7%)	
Advanced secondary or partial university	421 (51.4%)	1701 (51.9%)		67 (59.8%)	243 (54.2%)	
Complete university	101 (12.3%)	421 (12.9%)		7 (6.3%)	43 (9.6%)	
Positive atopic family history	46 (5.6%)	131 (4.0%)	0.042	6 (5.4%)	20 (4.5%)	0.688
Number of other children in household			0.580			0.006
0	479 (58.5%)	1970 (60.2%)		48 (42.9%)	262 (58.5%)	
1	265 (32.4%)	998 (30.5%)		47 (42.0%)	149 (33.3%)	
≥ 2	75 (9.2%)	307 (9.4%)		17 (15.2%)	37 (8.3%)	
Maternal smoking during pregnancy	21 (2.6%)	87 (2.7%)	0.574	3 (2.7%)	11 (2.5%)	0.892
Male sex	499 (60.9%)	1713 (52.3%)	< 0.001	79 (70.5%)	241 (53.8%)	0.001
Birth weight (g)	3496 $\pm$ 446	3434 $\pm$ 420	< 0.001	3429 $\pm$ 443	3415 $\pm$ 419	0.756
Gestational age (weeks)	39.4 $\dagger$ $\pm$ 1.0	39.4 $\dagger$ $\pm$ 1.0	0.050 $\dagger$	39.3 $\pm$ 1.2	39.3 $\pm$ 1.0	0.756
5-min Apgar score	8.5 $\pm$ 0.6	8.5 $\pm$ 0.6	0.975	8.4 $\pm$ 0.7	8.4 $\pm$ 0.6	0.611

*Categorical variables described using %, continuous variables using mean ($\pm$ SD). $\dagger$ The unrounded means were 39.37 and 39.44 weeks in the cases and controls, respectively.

For GI infection and atopic eczema, 61 (7.4%) of the 819 cases were exposed vs. 197 (6.0%) of the 3276 matched controls, for a crude matched OR of 1.27 (95% CI = 0.94–1.71). The adjusted OR was virtually unchanged [1.27 (0.94–1.72)]. For respiratory infection and atopic eczema, 288 (35.2%) of the 819 cases were exposed vs. 1067 (32.6%) of the 3276 matched controls, for a crude matched OR of 1.17 (0.97–1.40) and virtually identical adjusted OR [1.14 (0.94–1.37)].

For recurrent wheeze, 11 (9.8%) of the 112 cases were exposed to one or more prior episodes of GI infection vs. 33 (7.4%) of the 448 matched controls, for a crude matched OR of 1.37 (0.67–2.78) and an adjusted OR of 1.30 (0.60–2.82).

Discussion

The prevalence of atopic disease varies widely among populations and appears highest in those of higher socio-economic status, stricter hygienic standards, and better medical care [2]. For example, asthma and allergic rhinitis (AR) (hayfever) were far more common in West Germany than in East Germany prior to reunification [1]. Similarly, Chinese children living in mainland China have a lower prevalence of asthma and of skin-test hypersensitivity than children of similar origin living in Hong Kong, while those living in Malaysia fall in an intermediate position [3]. The hygiene hypothesis is also consistent with the extremely high prevalence of asthma in Tristan da Cunha [15, 16] and the Western Carolinas [17, 18], two isolated, highly inbred island communities with a low incidence of respiratory and other viral infections, but a high prevalence of intestinal parasitic infestation.

These findings are further supported by studies of children who migrated from developing to developed country settings; these studies have observed a much higher prevalence of asthma and atopy among the migrants than among children from the same countries who remained in their country of origin [18, 19]. Within-country studies have added further support by finding a lower prevalence of atopy (positive skin-prick tests) in British children with older siblings [20]; German children with earlier attendance at day care [4]; Swedish children from families following a so-called 'anthroposophic' life style (low rates of immunization, infrequent use of antibiotics and consumption of lactobacillus-rich fermented vegetables) [21]; European, Canadian, and Finnish children living on farms [5, 22, 23]; and children from Guinea-Bissau who received BCG vaccination [24]. Similarly, American children exposed to older siblings or other children at day care were found to be at lower risk of developing asthma and frequent wheezing by age 6–13 years [25].

These epidemiologic findings have given rise to the so-called 'hygiene hypothesis', whereby early infection steers Th lymphocytes toward the Th1 pathway (production of IgG antibodies, INF- γ , and IL-2) and away from the Th2 pathway (production of IgE and IL-4, -5, and -13) [8, 9, 11]. The hygiene hypothesis does not, however, explain the high prevalence of asthma among the inner-city US Blacks [26, 27], the increased risk of atopic eczema, AR, and asthma among Finnish children with a history of natural measles infection [28], nor the positive association between air pollution and atopic eczema in German preschool children [29]. Moreover,

a recent study found Th2-skewed T cell responses to common environmental antigens in cord blood from infants regardless of their atopic family history [30]. The potential protective, sensitizing, or triggering effects of early infections may depend on their viral vs. bacterial aetiology and their precise timing relative to antigen exposure [31–33]. Thus, viral respiratory infections in infancy, especially those caused by respiratory syncytial virus, have been linked to asthma in later childhood [31, 34].

Belarus is a country with a low incidence of infectious morbidity (e.g. among control infants in PROBIT [12], ≥ 1 episode of GI infection occurred in only 13.2%, and ≥ 2 episodes of respiratory infection in only 39%). The water supply is uncontaminated by bacterial enteropathogens, as ensured and regularly monitored throughout the Republic by public health authorities. Family sizes are small (the total fertility rate was 1.4 per woman in 1998) [35], the standard maternity leave is 3 years, and no day care centres are available for children under the age of 3 years. Such conditions are not very conducive to the spread of infectious disease. In this low-risk setting, neither GI nor respiratory infection appears to protect Belarussian infants against subsequent atopic eczema in the first 12 months of life. Nor does GI infection protect against subsequent recurrent wheeze during the same time period.

Although our results do not provide support for the role of early infection in protecting against atopic eczema or recurrent wheeze during infancy, we did not measure air pollution, aeroallergens, or exposure to farms, barn animals, or other non-infectious agents in the air or water supply. It is therefore possible that residual confounding by these unmeasured environmental variables may have biased the studied association towards the null. It is also possible that some episodes of GI symptoms classified as infection by our algorithm were allergic in origin, as reported by Caffarelli et al. [36], as only a very small fraction of our study infants classified as having GI infection were reported to be febrile and no culture or serology specimens were collected. Unlike the study of Caffarelli et al., however, our design ensured that episodes classified as GI infection preceded the onset of atopic eczema.

The relevance of atopic eczema and recurrent wheeze during infancy to the hygiene hypothesis merits comment. We are aware of only two previous investigations of early infection and atopic eczema: a recently published small Finnish study that reported a non-significant protective effect of respiratory infection [37] and a large British birth cohort study that found no protective effect of respiratory or GI infections [38]. For recurrent wheeze in the first 12 months of life, the relationship to subsequent asthma (and to atopy in general) is far from clear [31–34]. Indeed, our recurrent wheeze cases and controls did not differ significantly with respect to positive (first-degree) family history of atopy. The possible protective effect of early infection has been studied more frequently in relation to longer-term atopic outcomes such as asthma and skin-test hypersensitivity to aeroallergens. Future follow-up of the PROBIT cohort will provide extensive data about these associations, although the low prevalence of positive atopic family history (see Table 1) suggests that the incidence of atopic outcomes is likely to be low. Moreover, the absence of a protective effect of preceding

infection *within* the population of Belarus may not be generalizable to explaining differences *among* populations with differences in incidence of atopic eczema, recurrent wheeze, and infection during infancy. Whatever the explanation, alternative hypotheses for explaining the simultaneously low incidence of early infection and atopic disease in Belarus and other similar settings seem worthy of further study.

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