ORIGINAL ARTICLE

Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants

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Background: The hygiene hypothesis states that insufficient exposure to certain infectious agents during childhood increases the risk of developing asthma and atopic diseases. Improvements in hygiene levels may be partly responsible for this decline in exposure.
Aims: To assess whether hygiene levels in infancy are associated with wheeze and/or atopic eczema, independent of a number of possible confounding factors.
Methods: Data were gathered from the Avon Longitudinal Study of Parents and Children (ALSPAC). Parental self completion questionnaires provided symptom data on infant wheeze and atopic eczema at 0–6 months and 30–42 months, respectively. A simple hygiene score was derived using questionnaire responses at 15 months, which ranged from least hygienic to most hygienic. Multivariable logistic regression models analysed the effect of hygiene scores on health outcomes, while adjusting for a number of important confounding variables.
Results: Increasing hygiene scores were independently associated with wheezing (OR = 1.04; 95% CI: 1.00 to 1.08) and atopic eczema (OR = 1.04; 95% CI: 1.01 to 1.07) between 30 and 42 months, but not in the first six months. The odds ratio was higher for atopic eczema if the rash was reported to have become sore and oozy (OR = 1.09; 95% CI: 1.02 to 1.16).
Conclusions: High levels of hygiene at 15 months of age were independently associated with wheeze and atopic eczema reported between 30 and 42 months, and there was an increased risk for children with more severe eczema during this period. The importance of hygiene in public health should not be dismissed; however, the creation of a sterile environment through excessive cleanliness may potentially be harmful to the immune system.

Asthma, atopy, and other allergic diseases are diseases of the immune system. These diseases have been increasing in prevalence over the past three decades, particularly in the more affluent Westernised regions of the world.[1–3] There is immunological evidence to show that lack of exposure to certain types of infectious agents and endotoxins in childhood could lead to imbalanced Th-1 and Th-2 immune responses. This imbalance would typically favour a Th-2 response known to be a key mediator in allergic reactions.[4]

Epidemiological studies have shown that older siblings (particularly if they are boys),[5] attendance at day care,[6] living on a livestock farm,[7] or owning a furry pet[8] confer varying degrees of protection against the development of atopy. One possible explanation for this is that close contact with other children who may be carrying infections or direct exposure to infectious agents early enough in childhood somehow primes the immune system to behave normally. It has been proposed, therefore, that improvements in hygiene, despite being responsible for dramatic reductions in infection related mortality and morbidity in the past, may now be responsible for the rise in the prevalence of atopic diseases. This is known as the "hygiene hypothesis".[9]

In this study we investigated whether there is a direct association between levels of infant hygiene in the home and wheeze and atopic eczema in children under 3.5 years of age. In the accompanying paper,[10] a number of social, lifestyle, and environmental factors were found to be associated with the adoption of certain hygiene practices. One important factor was the frequency of use of chemical household products, which was higher in mothers who kept their infants very clean. Use of these products has been associated with the precipitation or exacerbation of respiratory symptoms and allergies,[11 12] and may have a potential confounding role in any association between hygiene and ill health.

METHODS

A full description of the ALSPAC study[13] is given in the accompanying paper,[10] including details on the production of the hygiene scores and on the confounding factors used in the current study. The hygiene scores ranged from 2 (least hygienic) to 14 (most hygienic) and were approximately normally distributed with a mean of 9 and a standard deviation of 2.

Health outcomes

On an annual basis, parents answered identical health related questions about their study child. For this study, responses to the following questions between birth and 6 months, and again between 30 and 42 months were analysed: Since birth [0–6 months]/In the last 12 months [30–42 months]:

(1) "Has your baby had wheezing with whistling on his/her chest when he/she breathed?"

(2) "Has the baby had a rash in the joints and creases of his/her body (e.g. behind the knees, under the arms)?" [at 42 months the word "itchy" was included before rash].

At 42 months there was a supplemental question to (2) which asked if the rash had ever become sore and oozy.

In this paper, a positive response to question (2) will be referred to as atopic eczema. For the period 30–42 months, validation studies have shown that question (2) identifies well clinical cases of atopic eczema,[14] but no such validation studies have been carried out for this rash occurring in the period 0–6 months. Nevertheless, positive answers to question (2) at

Table 1 Prevalence (% (n)) of wheezing and atopic eczema at 0–6 months and 30–42 months

Symptoms	Time period	
	0–6 months	30–42 months
Wheezing with whistling on the chest*	19.9 (2266)	13.4 (1343)
(Itchy) rash in joints and creases of body†	22.6 (2580)	22.7 (2265)
Rash becoming sore and oozy‡	N/A	5.2 (515)

*Wheezing at 6 months: n=11410; at 42 months: 9996.
†Atopic eczema at 6 months: n=11405; at 42 months: 9995.
‡Severe atopic eczema at 42 months: n=9904.

Table 2 Frequencies (% (n)) of hands and face washing and bathing and showering in 15 month old children

Hygiene question	Responses				
How often in a normal day:	Not at all	1–2 times	3–4 times	5 or more times	
Is his/her face washed	0.2 (23)	28.4 (3127)	60.8 (6711)	10.6 (1166)	
Are his/her hands washed/wiped	0.05 (5)	13.4 (1475)	62.2 (6862)	24.3 (2684)	
How often in a normal day:	Never	Occasionally	Sometimes	Usually	Always
Are hands cleaned before meals	5.5 (604)	14.6 (1615)	29.1 (3209)	36.3 (4017)	14.5 (1600)
How often does he/she usually:	Hardly ever	Once a week	Several times a week	Once every day	More than once a day
Have a bath or shower	0.1 (13)	4.2 (460)	35.5 (3912)	54.8 (6046)	5.4 (599)

Table 3 Unadjusted and adjusted odds ratios and 95% confidence intervals for period prevalence of wheeze and atopic eczema at 6 and 42 months according to a continuous hygiene score measured at 15 months

	Model 1*			Model 2†			Model 3‡		
Health outcome	n	OR (95% CI)	p	n	OR (95% CI)	p	n	OR (95% CI)	p
Wheezing with whistling on the chest									
0–6 months	10236	1.04 (1.02 to 1.07)	0.002	8357	1.01 (0.98 to 1.04)	0.7	7425	0.99 (0.97 to 1.03)	0.9
30–42 months	9334	1.05 (1.02 to 1.09)	0.002	8226	1.03 (0.99 to 1.07)	0.06	7319	1.04 (1.00 to 1.08)	0.03
Rash in joints and creases of body (atopic eczema)									
0–6 months	10233	0.99 (0.97 to 1.02)	0.5	8358	0.99 (0.97 to 1.02)	0.6	7424	0.99 (0.97 to 1.03)	0.9
30–42 months	9329	1.02 (0.99 to 1.05)	0.1	8215	1.02 (0.99 to 1.05)	0.2	7305	1.04 (1.01 to 1.07)	0.01
Rash becomes sore and oozy (severe atopic eczema)									
30–42 months	9317	1.06 (1.01 to 1.11)	0.03	8205	1.07 (1.02 to 1.13)	0.03	7296	1.09 (1.02 to 1.16)	0.007

*Unadjusted OR (95% CI).
†OR (95% CI) adjusted for frequency of use of chemical household products at 8 and 47 months only.
‡OR (95% CI) adjusted for frequency of use of chemical household products, maternal smoking during pregnancy, maternal education, housing tenure, damp housing, environmental tobacco smoke, gender, maternal parity, paracetamol use, attendance at daycare, contact with pets, maternal asthma (for wheeze outcomes), maternal eczema (for rash outcomes), and month of returning hygiene questionnaire.

6 months were strongly predictive of point prevalence of eczema on examination at 5 years of age (Michael Perkin, personal communication). If the parent responded that the rash (30–42 months) had become sore or oozy, the atopic eczema was considered to be clinically more severe (Dr Giles Dunnill, personal communication).

Statistical analysis

All data analyses were undertaken using binary logistic regression modelling within SPSS for Windows (version 9.0.0).

Three groups of models were produced for the period prevalence of all health outcomes between 0 and 6 months, and between 30 and 42 months. The first models were univariable analyses of the association between health outcome (wheeze, atopic eczema) and hygiene score (model 1). The second group of models analysed health outcome in terms of the hygiene score, adjusting for the frequency of use of chemical household products only (model 2). The final group of models of health outcome and hygiene score adjusted for all possible confounding variables (model 3).

RESULTS

Table 1 presents period prevalences of wheezing and atopic eczema for the periods 0–6 months and 30–42 months. Table 2 presents frequencies of hands and face washing and bathing and showering in the 15 months old children. In total, 10 970 children had sufficient data for the derivation of a hygiene score. Table 3 presents the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) for wheeze and atopic eczema.

Wheezing with whistling on the chest

The odds ratios for wheezing at 0–6 months and 30–42 months increased significantly with increasing hygiene scores within the unadjusted models (table 3, model 1). However, it appeared that this association in the children who wheezed at 0–6 months could be explained by the fact that children with high hygiene scores were more likely to have mothers who made frequent use of chemical household products (table 3, model 2). Once the model had been adjusted for frequency of use of chemical household products, the odds ratio for wheeze at 0–6 months was much reduced and no longer statistically

significant. Frequency of use of chemical household products also attenuated the effect of hygiene score on wheeze reported at 30–42 months, but to a lesser degree. Thus, after adjustment for frequency of use of chemical household products, for every unit increase in hygiene score, the odds ratio for wheeze at 30–42 months increased by 3%, an effect which was of borderline significance (p = 0.06) (table 3, model 2).

In the fully adjusted models (table 3, model 3) an increase in hygiene score of one unit was significantly and independently associated with a 4% increase in the odds ratio of wheeze at 30–42 months (OR = 1.04; 95% CI: 1.00 to 1.08), but had no significant effect on early infant wheeze (p = 0.9).

Atopic eczema

In the unadjusted models (model 1), only severe atopic eczema at 30–42 months was significantly associated with hygiene score (OR = 1.06; 95% CI: 1.01 to 1.11; p = 0.03). Unlike wheeze, the effect of hygiene on atopic eczema reported at 0–6 months or 30–42 months was relatively unaffected by the inclusion of frequency of use of chemical household products into the models (model 2). In the fully adjusted models (model 3), there was a significant independent association between atopic eczema and hygiene score (OR = 1.04; 95% CI: 1.01 to 1.07; p = 0.01) which increased when the analysis was confined to those children with severe atopic eczema (OR = 1.09; 95% CI: 1.02 to 1.16; p = 0.007).

DISCUSSION

Within this contemporary population in the UK there is a wide range of infant hygiene practices. This study has found that increasing levels of hygiene are associated with wheezing and atopic eczema occurring between 30 and 42 months of age, but not in the first six months after birth. There was a stronger association with hygiene score in children with more severe atopic eczema (30–42 months). These findings were independent of a number of factors considered to be potential confounders in the association between hygiene and atopy, and provide further support for the hygiene hypothesis.[9]

Participants in the ALSPAC study are broadly representative of the general population of Avon in terms of sociodemographic and lifestyle factors. There is, however, a shortfall of ethnic groups participating in the study and of families in the more socially disadvantaged groups. The prevalences of wheeze and atopic eczema were similar for children who had data on hygiene practices and for those who did not. Similarly, those without health data had similar hygiene scores to those with health data. Therefore it did not appear that there was any major selection bias in the study sample.

In this study atopic eczema has been defined as the presence of a rash in the joints and creases of the body at 0–6 months and/or at 30–42 months. For the latter duration, the UK working party has verified this definition and found it to be 74% specific and 90% sensitive.[14] However for the former duration (0–6 months), this definition has not been tested clinically. It is possible that other conditions, such as seborrhoeic dermatitis, may also be included in the group with a positive response to this question, but the strong predictive value of rash at this age with clinical evidence of eczema at age 5 suggests that the bulk of positive responses at this age were indeed of atopic eczema.

There was some concern that within the group of children with atopic eczema, there would be a greater propensity to wash more frequently owing to the nature of the condition, and even more so if the rash was sore and oozy. Because of the longitudinal nature of this study, there was scope to analyse only those children who developed atopic eczema subsequent to the return of the questionnaire on hygiene practices. Children who had atopic eczema at 30–42 months but not at 0–6 months were compared to those who never had eczema during either study period. In the fully adjusted model, the effect of hygiene on atopic eczema remained statistically significant with a similar odds ratio to the original analysis (adjusted OR = 1.04; 95% CI: 1.00 to 1.08; p = 0.03). A similar result was obtained on examining only those children who had reported severe atopic eczema at 30–42 months but not at 0–6 months (adjusted OR = 1.07; 95% CI: 0.97 to 1.2). In this case, however, despite comparable odds ratios between the subanalysis and the full analysis, there was insufficient power (as a result of small numbers, n = 180) to detect this odds ratio as statistically significant.

There is some evidence to show that excessive hands washing may lead to atopic eczema in adults.[15] To determine whether the association between atopic eczema and hygiene may have been due in some part to excessive hands washing, we explored whether children with severe atopic eczema (30–42 months) more frequently washed their hands than children without the condition. We found no statistical evidence that this was the case: 24.1% of children without severe atopic eczema had their hands washed five or more times per day compared to 25.6% of children with severe atopic eczema (Fisher's exact test: p = 0.3).

As wheezing symptoms are highly correlated with eczema, particularly in older children, an additional analysis was carried out to determine whether the effect of hygiene on wheeze was independent of the fact that many children who wheeze also have symptoms of eczema. Model 3 for wheeze at 30–42 months (table 3) was reproduced, this time adjusting for whether the child was also reported to have eczema during this period. The effect did not change appreciably (adjusted OR = 1.04; 95% CI: 1.00 to 1.08). Thus, the effect of hygiene on the prevalence of wheeze during the period 30–42 months was not confounded by the fact that the child may also have had atopic eczema.

A possible explanation for the positive association between hygiene and wheeze and atopic eczema is that children with high hygiene scores would have less contact with infectious agents than their less hygienic peers as a result of increased hands and face washing, bathing, and showering. Alternatively, high hygiene scores may reflect a difference in behaviour that would reduce this exposure to infectious agents, such as less outdoor play or reduced contact with other children. This increased risk of atopy in the hygienic children is in accord with the hypothesis that early exposure to infections somehow protects against allergies in later life.

We did not show an association between high hygiene scores and wheeze or atopic eczema in the first six months. This may reflect the heterogeneous nature of early life respiratory symptoms and rash—many cases of which are not atopic.

We cannot rule out the possibility that hygiene levels are acting as a proxy measure for some other, as yet unmeasured, risk factor that is not associated with the hygiene hypothesis. To date this is the first epidemiological study which has related infant hygiene to possible markers of atopy. The results provide some support for the hygiene hypothesis but require replication and further investigation of the ALSPAC cohort, using more objective measures of atopy such as established genetic polymorphisms for atopy, skin prick allergy tests, and total and specific IgE concentrations.

Conclusion

In this study we have established an independent association between infant hygiene score and both wheeze and atopic eczema reported during the period 30–42 months, which supports the hygiene hypothesis. These results are not significantly attenuated or mediated by increased use of chemical household products, nor are they affected by other social, maternal, or environmental factors known to be important in the aetiology of atopic disorders. However, this is not to say that some as yet unmeasured factor for which hygiene may be a proxy is responsible for the observed associations. The

importance of hygiene in public health should not be dismissed; however, the creation of a sterile environment through excessive cleanliness may potentially be harmful to the immune system. Future refinement of the atopic phenotype using genetic polymorphisms obtained from the DNA of these children and more objective markers of atopy such as skin prick allergy tests and total and specific IgE concentrations will help elucidate features of the complex aetiology of atopic disorders.

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