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Strachan, DP; Ait-Khaled, N; Foliaki, S; Mallol, J; Odhiambo, J; Pearce, N; Williams, HC; ISAAC Phase Three Study Group; (2014) Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clinical and experimental allergy*, 45 (1). pp. 126-36. ISSN 0954-7894 DOI: <https://doi.org/10.1111/cea.12349>

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# Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood

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## Clinical & Experimental Allergy

### Summary

**Background** Associations of larger families with lower prevalences of hay fever, eczema and objective markers of allergic sensitization have been found fairly consistently in affluent countries, but little is known about these relationships in less affluent countries.

**Methods** Questionnaire data for 210 200 children aged 6–7 years from 31 countries, and 337 226 children aged 13–14 years from 52 countries, were collected by Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). Associations of disease symptoms and labels of asthma, rhinoconjunctivitis and eczema were analysed by numbers of total, older and younger siblings, using mixed (multi-level) logistic regression models to adjust for individual covariates and at the centre level for region, language and national affluence.

**Results** In both age groups, inverse trends ( $P < 0.0001$ ) were observed for reported 'hay fever ever' and 'eczema ever' with increasing numbers of total siblings, and more specifically older siblings. These inverse associations were significantly ( $P < 0.005$ ) stronger in more affluent countries. In contrast, symptoms of severe asthma and severe eczema were positively associated ( $P < 0.0001$ ) with total sibship size in both age groups. These associations with disease severity were largely independent of position within the sibship and national GNI per capita.

**Conclusions** These global findings on sibship size and childhood asthma, rhinoconjunctivitis and eczema suggest at least two distinct trends. Inverse associations with older siblings (observations which prompted the 'hygiene hypothesis' for allergic disease) are mainly a phenomenon of more affluent countries, whereas greater severity of symptoms in larger families is globally more widespread.

**Keywords** allergic rhinitis, asthma, atopic dermatitis, birth order, eczema, hay fever, international, siblings

Submitted 18 November 2013; revised 6 April 2014; accepted 13 May 2014

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Cite this as: D. P. Strachan, N. Ait-Khaled, S. Foliaki, J. Mallol, J. Odhiambo, N. Pearce, H. C. Williams and the ISAAC Phase Three Study Group, *Clinical & Experimental Allergy*, 2015 (45) 126–136.

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### Introduction

More than two decades have elapsed as an inverse association was reported between numbers of siblings (particularly older siblings) and the parentally reported

prevalence of hay fever and eczema in two British national cohorts, born in 1970 [1] and 1958 [2]. These observations, since replicated very widely in affluent countries [3–27], prompted the hypothesis that the rising prevalence of allergic diseases may be due to a reduction in exposure to infections in modern industrialized societies [2].

The epidemiological associations which underpin this 'hygiene hypothesis' have not been studied so extensively

\*ISAAC Phase Three Study Group members are presented in the Appendix 1.

†Died 27 October 2012.

in less affluent countries. The International Study of Asthma and Allergies in Childhood (ISAAC, <http://isaac.auckland.ac.nz/>) provides a unique global perspective on asthma, rhinoconjunctivitis and eczema. In this paper, we present the associations of sibship size and position within the sibship with both current symptoms and life-time labelling of these three conditions, among both younger and older children.

## Methods

Phase Three of ISAAC has been described in detail elsewhere [28]. In brief, each study centre performed a cross-sectional questionnaire survey of 13 to 14-year-old adolescents and (optionally) 6 to 7-year-old children, using a cluster sample design with schools as the primary sampling unit (cluster). Parents completed written questionnaires on behalf of the younger children, while the adolescents completed written questionnaires themselves at school. Questionnaires were translated from English into the local language and back-translated for validation prior to fieldwork. Ethics committee approvals were obtained locally.

Symptom prevalence, severity and disease labels were ascertained by the ISAAC core symptom questionnaires [28]. Following conventions set in previous ISAAC Phase Three analyses, the following combinations of responses were used to define 'current' and 'severe' symptoms of asthma, rhinoconjunctivitis and eczema:

- Current asthma symptoms: wheezing or whistling in the chest in the past 12 months.
- Severe asthma symptoms: in the past 12 months, *either* four or more attacks of wheezing *and/or* sleep disturbed due to wheezing one or more nights per week on average *and/or* wheeze-limiting speech to only one or two words at a time between breaths.
- Current rhinoconjunctivitis: in the past 12 months, a problem with sneezing, or a runny or blocked nose when you/he/she did not have a cold or the 'flu, *and* this nose problem was accompanied by itchy watery eyes.
- Severe rhinoconjunctivitis: In the past 12 months, this nose problem interfered with daily activities a lot.
- Current eczema symptoms: an itchy rash which at any time was coming and going for at least 6 months had at any time affected the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes, and was present at any time in the past 12 months.
- Severe eczema symptoms: in the past 12 months, kept awake at night one or more nights per week on average by this itchy rash.

Additional analyses were carried out for lifetime histories (as reported in the cross-sectional survey) of wheeze, non-infective rhinitis, itchy rash, asthma, hay

fever and eczema. These correspond to the first and last questions within each section of the core questionnaire and were asked of all subjects (i.e. without stem-and-branch structure):

- Wheeze ever: ever had wheezing or whistling in the chest.
- Asthma ever: ever had asthma.
- Rhinitis ever: ever had a problem with sneezing, or a runny or blocked nose when you/he/she did not have a cold or the 'flu.
- Hay fever ever: ever had hay fever.
- Itchy rash ever: ever had an itchy rash which at any time was coming and going for at least 6 months.
- Eczema ever: ever had eczema.

The symptom questionnaire was followed (at the discretion of the study centre) by a risk factor ('environmental') questionnaire which included questions about the number of older brothers and sisters, and younger brothers and sisters. These were combined into a 'total siblings' variable for analysis. Numbers of total, older and younger siblings were each analysed in four groups (0, 1, 2, 3 or more) for the purposes of both categorical and trend analyses. When assessing the trend in prevalence by number of older siblings, the number of younger siblings was included as a categorical covariate, and vice versa. Centres where more than 30% of children had missing data on sibship size were excluded from the analysis.

Statistical analyses used a two-level multiple logistic regression model, implemented in SAS PROC GLIMMIX (SAS Institute Inc., Cary, NC, USA). This allowed simultaneous adjustment for both individual-level and centre-level covariates. Basic analyses adjusted for gender at the individual level and for WHO region, language and national affluence at the centre level. Affluence was measured by the World Bank 2001 statistics on Gross National Income (GNI) per person [29]. Following conventions set by previous ISAAC Phase Three analyses, adjustments were made to the effective sample size (design effect) for each symptom or disease outcome, based on the within-school (intra-cluster) correlation observed for each outcome within each centre and age group.

Due to the large sample sizes in each age group and the multiple inter-related comparisons being made, the presentation and discussion will focus upon results that are significant at the 1% level ( $P < 0.01$ ) and particularly on those significant at the 0.01% level ( $P < 0.0001$ ).

## Results

Information about sibship size and symptoms was available for 210 200 children aged 6–7 years from 74 centres in 31 countries, and for 337 226 adolescents

aged 13–14 years from 116 centres in 52 countries. In the younger age group, 17% of children had no brothers or sisters, 44% had one, 23% had two and 17% had three or more siblings. Among the adolescents, the corresponding figures were 11%, 32%, 25% and 32%, respectively.

When the centres were subdivided according to national per capita income (GNI, using the World Bank 2001 classification of 'high' vs. the remainder), the younger age group comprised 67 026 children from 24 centres in 10 affluent countries and 143 174 children from 50 centres in 21 less affluent countries. The older age group comprised 101 082 adolescents from 33 centres in 16 affluent countries and 236 144 adolescents from 83 centres in 36 less affluent countries. Most of the affluent countries are located at latitudes where seasonal fluctuations in outdoor aeroallergen levels are expected, whereas many of the less affluent countries lie within the tropics, where the concept of hay fever or seasonal allergic rhinitis may be less relevant.

Table 1 shows the association between total number of siblings and each symptom or disease outcome, for each age group, expressed both as comparisons with the zero siblings group and as a significance test for trend in odds ratios. Highly significant ( $P < 0.0001$ ) trends of lower prevalence with increasing sibship size were observed in both age groups for a lifetime history of hay fever and for a lifetime history of eczema, with a less significant ( $P < 0.001$ ) trend for asthma ever in the adolescents, but not for asthma ever in the younger age group. In contrast, children with more siblings were less likely to have a history of wheeze ever in both age groups, whereas the inverse associations with rhinitis ever and with itchy rash ever were not consistent between younger children and adolescents. Although current symptoms were generally not significantly associated with sibship size, the exception was current flexural dermatitis which showed a trend ( $P < 0.01$ ) to be more common in larger families. However, severe asthma symptoms and severe eczema symptoms were highly significantly ( $P < 0.0001$ ) associated with larger sibships, in both age groups. The association of sibship size with severe rhinoconjunctivitis was weaker and not significant at the 1% level in either age group.

Table 2 shows the odds ratios associated with each additional older sibling, adjusting for the number of younger siblings (as a categorical covariate) and vice versa. The inverse associations of total siblings with hay fever ever and with eczema ever were more strongly influenced by older siblings: relative reductions of about 10% per older sibling in the younger age group and about 5% per older sibling in the adolescents. These effects of position within the sibship were highly significant, after adjustment for the number of younger siblings (thus, independent of total sibship

size). In the older age group, there was a weaker 'protective' influence of younger siblings, independent of older siblings, a trend which was statistically significant ( $P < 0.01$ ) for hay fever but not for eczema. The inverse trend with younger siblings was significantly weaker than the trend with older siblings for eczema ever in the children, and for hay fever ever in both age groups. In contrast, the increased risk of severe asthma and severe eczema symptoms in larger families was attributable in approximately equal measure to older and to younger siblings (Table 2). There were no significant differences between the effects of older and younger siblings on these more severe symptoms.

Table 3 compares the per-sibling odds ratios from the total sibship size analyses for centres in affluent countries and centres in non-affluent countries. Generally, the inverse associations with disease labels were concentrated mainly in the affluent countries, whereas the positive associations with disease severity were found in both affluent and non-affluent countries. There were significant differences ( $P < 0.001$ ) between affluent and non-affluent centres for the sibship size effects on hay fever ever and eczema ever in both age groups.

Table 4 explores the association of total sibship size with current and severe symptoms, after stratifying the children according to the relevant disease label (asthma ever for asthma symptoms, hay fever ever for rhinoconjunctivitis and eczema ever for eczema symptoms). In both age groups, the associations of larger families with severe asthma and severe eczema were present both among children with the relevant disease label, and among children without this label. After stratification by disease label, these positive associations of severity with sibship size generally strengthened and became even more highly significant than in the unstratified analyses shown in the left-hand columns of Table 3.

Table 5 compares the effect of total siblings on each outcome before and after adjustment for a range of potential confounding variables in the younger age group. This analysis was restricted to the younger children because there were a wider range of covariates ascertained from the parental questionnaire, particularly those relating to early childhood. The following 'current exposures' were considered as confounders for total siblings – gender, maternal education, mother or father smoking currently (i.e. at age 6–7), current cat and dog ownership, truck traffic exposure and current cooking fuels. The following 'early-life' factors were considered as confounders for older siblings – gender, maternal education, mother smoking in the first year, cat, dog and farm animal exposure in the first year, birth weight, breastfeeding, paracetamol use in the first year and antibiotic use in the first year.

The results shown in Table 5 are derived from 135 250 six to seven-year-old children with complete

Table 1. Association of symptoms and disease labels with total number of siblings, odds ratios by category and test for trend

	No siblings OR (95% CL)	One sibling (vs. none) OR (95% CL)	Two siblings (vs. none) OR (95% CL)	Three or more siblings (vs. none) OR (95% CL)	Trend <i>P</i> value
Symptom (6 to 7-year-olds)					
Wheeze ever	1.00 (reference)	0.99 (0.95, 1.03)	0.93 (0.89, 0.98)	0.89 (0.84, 0.94)	< 0.0001
Wheeze in last 12 months	1.00 (reference)	0.99 (0.94, 1.04)	0.96 (0.91, 1.02)	0.99 (0.92, 1.05)	0.35
Severe wheeze in last 12 months	1.00 (reference)	0.99 (0.92, 1.07)	1.05 (0.97, 1.14)	1.19 (1.09, 1.30)	< 0.0001
Asthma ever	1.00 (reference)	1.02 (0.97, 1.08)	0.95 (0.89, 1.01)	0.98 (0.92, 1.05)	0.11
Rhinitis ever	1.00 (reference)	0.96 (0.92, 1.00)	0.87 (0.83, 0.91)	0.86 (0.82, 0.90)	< 0.0001
Rhinoconjunctivitis in last 12 months	1.00 (reference)	1.00 (0.95, 1.06)	0.95 (0.90, 1.01)	0.96 (0.90, 1.04)	0.09
Severe rhinoconjunctivitis	1.00 (reference)	1.03 (0.86, 1.23)	1.01 (0.83, 1.23)	1.15 (0.92, 1.43)	0.32
Hay fever ever	1.00 (reference)	0.97 (0.91, 1.02)	0.85 (0.79, 0.90)	0.81 (0.75, 0.87)	< 0.0001
Itchy rash ever	1.00 (reference)	1.04 (1.00, 1.09)	1.00 (0.95, 1.05)	1.02 (0.96, 1.08)	0.82
Itchy flexural rash in last 12 months	1.00 (reference)	1.09 (1.03, 1.15)	1.01 (0.95, 1.08)	1.04 (0.97, 1.12)	0.91
Severe itchy flexural rash	1.00 (reference)	1.04 (0.89, 1.22)	1.14 (0.96, 1.35)	1.63 (1.36, 1.95)	< 0.0001
Eczema ever	1.00 (reference)	1.03 (0.98, 1.08)	0.92 (0.87, 0.97)	0.81 (0.75, 0.86)	< 0.0001
Symptom (13 to 14-year-olds)					
Wheeze ever	1.00 (reference)	0.94 (0.89, 0.99)	0.92 (0.87, 0.98)	0.90 (0.85, 0.96)	0.002
Wheeze in last 12 months	1.00 (reference)	0.96 (0.90, 1.03)	0.98 (0.92, 1.05)	0.97 (0.91, 1.04)	0.82
Severe wheeze in last 12 months	1.00 (reference)	0.96 (0.88, 1.03)	1.05 (0.97, 1.14)	1.14 (1.05, 1.24)	< 0.0001
Asthma ever	1.00 (reference)	0.96 (0.91, 1.02)	0.94 (0.89, 1.00)	0.91 (0.85, 0.96)	0.006
Rhinitis ever	1.00 (reference)	0.96 (0.91, 1.00)	0.94 (0.89, 0.99)	0.97 (0.92, 1.02)	0.58
Rhinoconjunctivitis in last 12 months	1.00 (reference)	0.97 (0.91, 1.03)	0.96 (0.90, 1.02)	1.03 (0.96, 1.09)	0.12
Severe rhinoconjunctivitis	1.00 (reference)	0.93 (0.78, 1.11)	0.89 (0.75, 1.07)	1.09 (0.91, 1.30)	0.07
Hay fever ever	1.00 (reference)	0.92 (0.86, 0.97)	0.86 (0.81, 0.91)	0.82 (0.77, 0.88)	< 0.0001
Itchy rash ever	1.00 (reference)	0.93 (0.88, 0.99)	0.94 (0.89, 1.00)	1.03 (0.97, 1.10)	0.009
Itchy flexural rash in last 12 months	1.00 (reference)	0.91 (0.85, 0.98)	0.96 (0.88, 1.03)	1.05 (0.97, 1.13)	0.001
Severe itchy flexural rash	1.00 (reference)	0.96 (0.81, 1.15)	1.09 (0.91, 1.30)	1.33 (1.11, 1.58)	< 0.0001
Eczema ever	1.00 (reference)	0.95 (0.89, 1.01)	0.90 (0.84, 0.96)	0.88 (0.82, 0.94)	< 0.0001

All analyses are adjusted for gender, region, language and national GNI per capita.

covariate data, from 55 centres in 21 countries. The patterns of unadjusted results were very similar in this subset, compared to the total sample, and the effect of adjustment was minimal, both for the total sibling effects and the associations with numbers of older siblings.

## Discussion

This study, of over half a million children from diverse study centres worldwide, provides the most comprehensive assessment to date of the association of symptoms of asthma, rhinoconjunctivitis and eczema with total number of siblings and with position within the sibship. The findings from adolescents and younger children were generally consistent and suggest at least two distinct trends. Inverse associations of total sibship size with disease labels (particularly for hay fever and eczema) are largely attributable to the number of older siblings and are mainly a phenomenon of more affluent countries. In contrast, the greater prevalence of more severe symptoms of asthma and eczema in larger families is globally more widespread, and related to total

numbers of brothers and sisters, rather than to position in the sibship.

The strengths of ISAAC lie in its size and the diversity of the participating centres. In such a large total sample size, quite subtle associations can be statistically significant at the conventional 5% level. We have concentrated on the more extreme *P* values and the strength of associations, and the more consistent and contrasting patterns across disease outcomes, age groups and study centres, ranked according to national GNI per capita.

An important limitation is that this ISAAC Phase Three study is based entirely on questionnaire data. However, in Phase Two of ISAAC, among 9 to 11-year-old children from 30 centres, in 22 countries worldwide (including seven non-affluent countries and three countries from Eastern Europe), written symptom questionnaires were supplemented by skin prick tests for sensitization to six common aeroallergens [30]. When skin prick test positivity to any allergen was analysed in relation to total number of siblings within each centre and combined by random-effects meta-analysis, the pooled odds ratio for skin test positivity per additional

Table 2. Association of symptoms and disease labels with numbers of older and younger siblings (mutually adjusted)

	Older siblings (per additional sibling) adjusted for younger siblings		Younger siblings (per additional sibling) adjusted for older siblings		Comparison of trends for older and younger siblings
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value	<i>P</i> value
Symptom (6 to 7-year-olds)					
Wheeze ever	0.97 (0.95, 0.98)	< 0.0001	0.96 (0.94, 0.98)	0.0003	0.82
Wheeze in last 12 months	1.01 (0.99, 1.03)	0.38	0.96 (0.93, 0.98)	0.0008	0.001
Severe wheeze in last 12 months	1.07 (1.04, 1.10)	< 0.0001	1.04 (1.01, 1.08)	0.02	0.25
Asthma ever	0.99 (0.97, 1.01)	0.27	0.98 (0.96, 1.01)	0.23	0.81
Rhinitis ever	0.93 (0.91, 0.94)	< 0.0001	1.03 (1.01, 1.05)	0.006	< 0.0001
Rhinoconjunctivitis in last 12 months	0.98 (0.96, 1.00)	0.03	1.03 (1.00, 1.06)	0.04	0.003
Severe rhinoconjunctivitis	1.00 (0.93, 1.07)	0.89	1.11 (1.02, 1.21)	0.01	0.05
Hay fever ever	0.91 (0.89, 0.93)	< 0.0001	1.00 (0.97, 1.02)	0.74	< 0.0001
Itchy rash ever	0.98 (0.96, 1.00)	0.02	1.06 (1.04, 1.09)	< 0.0001	< 0.0001
Itchy flexural rash in last 12 months	0.98 (0.96, 1.00)	0.09	1.06 (1.03, 1.09)	< 0.0001	< 0.0001
Severe itchy flexural rash	1.14 (1.08, 1.20)	< 0.0001	1.20 (1.12, 1.28)	< 0.0001	0.22
Eczema ever	0.90 (0.88, 0.92)	< 0.0001	1.03 (1.01, 1.06)	0.02	< 0.0001
Symptom (13 to 14-year-olds)					
Wheeze ever	0.97 (0.96, 0.99)	0.0005	0.99 (0.97, 1.01)	0.27	0.12
Wheeze in last 12 months	0.99 (0.97, 1.01)	0.26	1.10 (0.99, 1.03)	0.43	0.19
Severe wheeze in last 12 months	1.04 (1.02, 1.07)	0.0001	1.07 (1.04, 1.09)	< 0.0001	0.13
Asthma ever	0.97 (0.96, 0.99)	0.0003	0.99 (0.97, 1.01)	0.36	0.09
Rhinitis ever	1.00 (0.98, 1.01)	0.65	1.01 (0.99, 1.02)	0.50	0.41
Rhinoconjunctivitis in last 12 months	1.00 (0.99, 1.02)	0.71	1.03 (1.01, 1.05)	0.004	0.05
Severe rhinoconjunctivitis	1.03 (0.99, 1.08)	0.15	1.07 (1.02, 1.13)	0.004	0.24
Hay fever ever	0.94 (0.93, 0.96)	< 0.0001	0.97 (0.96, 0.99)	0.006	0.02
Itchy rash ever	1.02 (1.01, 1.04)	0.06	1.02 (1.00, 1.04)	0.03	0.81
Itchy flexural rash in last 12 months	1.03 (1.01, 1.05)	0.01	1.03 (1.01, 1.06)	0.004	0.66
Severe itchy flexural rash	1.12 (1.07, 1.16)	< 0.0001	1.10 (1.05, 1.14)	< 0.0001	0.55
Eczema ever	0.96 (0.95, 0.98)	< 0.0001	0.98 (0.96, 1.00)	0.06	0.28

All analyses are adjusted for sex, region, language and national GNI per capita.

sibling was 0.93 (95% CI 0.90–0.97). This is very similar to the corresponding per-sibling odds ratios for hay fever ever and eczema ever in Phase Three (Table 2), suggesting that the latter are not simply a labelling artefact, but evidence of an underlying biological effect, as reported in other studies [3, 27].

Sibship size is not necessarily the same as household size, and patterns of child contact may be influenced as much by local customs in child care and schooling as by the size of the household. What is meant by 'brother' and 'sister' may also be culturally determined. These uncertainties would tend to attenuate any true association with sibship size or position within the sibship, whereas the principal associations that we observed are not only strong but also display differences in their epidemiological patterns. There is a relative specificity of protective influences from older siblings, contrasting with similar adverse influences on severity from older and younger siblings.

The major confounding factors for older siblings and total siblings differ substantially, as biomedical influences associated with birth order are only weakly

correlated with total siblings, whereas most socioeconomic and lifestyle confounders that are correlated with total family size are not independently associated with position within the sibship. However, when our results were adjusted for a range of 'current' confounders (for total sibship size) and 'early-life' confounders (for older siblings), the trends remained virtually unchanged. Although measurement error in the covariates may have reduced the rigour of this adjustment, the robustness of the sibship size associations suggests that their underlying explanations lie in factors unrelated to those included in our models.

Most previous ISAAC reports have concentrated on current symptoms and selected measures of severity. We used the severity markers for asthma symptoms and eczema symptoms that were developed for earlier ISAAC publications [31, 32], and both of these include sleep disturbance. As it is possible that sleep may be disturbed by other children, particularly if they share a bedroom, we examined alternative measures of severity that excluded night waking. For instance, the odds ratio per additional sibling for one or more episodes of

Table 3. Association of total number of siblings with symptoms and disease labels in affluent and non-affluent centres

	Total siblings (per additional sibling) Affluent centres*		Total siblings (per additional sibling) Non-affluent centres*		Comparison of trends in affluent and non-affluent centres <i>P</i> value
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value	
Symptom (6 to 7-year-olds)					
Wheeze ever	0.94 (0.91, 0.96)	< 0.0001	0.98 (0.96, 1.00)	0.02	0.01
Wheeze in last 12 months	0.96 (0.93, 0.99)	0.007	1.01 (0.99, 1.04)	0.33	0.006
Severe wheeze in last 12 months	1.02 (0.98, 1.07)	0.36	1.09 (1.05, 1.13)	< 0.0001	0.03
Asthma ever	0.97 (0.94, 1.00)	0.08	0.99 (0.96, 1.02)	0.54	0.37
Rhinitis ever	0.92 (0.89, 0.94)	< 0.0001	0.96 (0.94, 0.98)	0.0001	0.002
Rhinoconjunctivitis in last 12 months	0.90 (0.87, 0.93)	< 0.0001	1.03 (1.01, 1.06)	0.02	< 0.0001
Severe rhinoconjunctivitis	0.99 (0.88, 1.12)	0.09	1.06 (0.97, 1.15)	0.18	0.39
Hay fever ever	0.87 (0.84, 0.91)	< 0.0001	0.96 (0.93, 0.99)	0.003	0.0001
Itchy rash ever	1.00 (0.97, 1.03)	0.88	1.00 (0.98, 1.02)	0.84	0.99
Itchy flexural rash in last 12 months	0.98 (0.95, 1.01)	0.24	1.01 (0.98, 1.04)	0.45	0.16
Severe itchy flexural rash	1.16 (1.05, 1.28)	0.003	1.18 (1.10, 1.27)	< 0.0001	0.80
Eczema ever	0.90 (0.88, 0.93)	< 0.0001	0.96 (0.93, 0.99)	0.005	0.003
Symptom (13 to 14-year-olds)					
Wheeze ever	0.99 (0.96, 1.02)	0.42	0.96 (0.94, 0.98)	0.0006	0.09
Wheeze in last 12 months	1.01 (0.98, 1.04)	0.49	0.99 (0.96, 1.01)	0.36	0.25
Severe wheeze in last 12 months	1.08 (1.04, 1.12)	0.0002	1.06 (1.03, 1.09)	0.0002	0.52
Asthma ever	0.96 (0.94, 0.99)	0.005	0.98 (0.95, 1.00)	0.03	0.45
Rhinitis ever	0.98 (0.95, 1.00)	0.05	1.10 (0.99, 1.03)	0.39	0.04
Rhinoconjunctivitis in last 12 months	1.00 (0.98, 1.03)	0.84	1.02 (1.00, 1.05)	0.08	0.33
Severe rhinoconjunctivitis	1.05 (0.95, 1.16)	0.36	1.05 (0.99, 1.11)	0.13	0.97
Hay fever ever	0.91 (0.88, 0.93)	< 0.0001	0.98 (0.95, 1.00)	0.07	0.0001
Itchy rash ever	0.99 (0.97, 1.02)	0.67	1.05 (1.02, 1.07)	0.0003	0.009
Itchy flexural rash in last 12 months	1.03 (1.00, 1.07)	0.09	1.04 (1.01, 1.07)	0.01	0.81
Severe itchy flexural rash	1.18 (1.08, 1.28)	0.0003	1.12 (1.06, 1.19)	< 0.0001	0.36
Eczema ever	0.93 (0.90, 0.95)	< 0.0001	1.00 (0.97, 1.03)	0.77	0.0006

\*Affluent centres: centres in countries with 'high' GNI per capita as defined by World Bank, 2001; Non-affluent centres: all other centres.

Table 4. Association of total number of siblings with symptoms in subjects with and without the relevant disease label

	Total siblings (per additional sibling) Subjects with relevant disease label ever*		Total siblings (per additional sibling) Subjects without relevant disease label ever*		Comparison of trends for subjects with and without relevant disease label <i>P</i> value
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value	
Symptom (6 to 7-year-olds)					
Wheeze in last 12 months	1.02 (0.98, 1.06)	0.36	0.98 (0.96, 1.01)	0.22	0.14
Severe wheeze in last 12 months	1.07 (1.03, 1.12)	0.0009	1.10 (1.05, 1.15)	< 0.0001	0.39
Rhinoconjunctivitis in last 12 months	1.00 (0.97, 1.04)	0.89	1.04 (1.01, 1.07)	0.01	0.14
Severe rhinoconjunctivitis	1.11 (1.02, 1.21)	0.01	1.06 (0.94, 1.19)	0.34	0.49
Itchy flexural rash in last 12 months	1.06 (1.02, 1.10)	0.001	1.02 (0.99, 1.05)	0.22	0.11
Severe itchy flexural rash	1.22 (1.13, 1.32)	< 0.0001	1.24 (1.13, 1.35)	< 0.0001	0.87
Symptom (13 to 14-year-olds)					
Wheeze in last 12 months	1.01 (0.98, 1.05)	0.55	1.02 (0.99, 1.04)	0.21	0.83
Severe wheeze in last 12 months	1.08 (1.04, 1.12)	< 0.0001	1.11 (1.07, 1.14)	< 0.0001	0.28
Rhinoconjunctivitis in last 12 months	1.04 (1.01, 1.07)	0.02	1.03 (1.01, 1.06)	0.009	0.78
Severe rhinoconjunctivitis	1.07 (1.01, 1.15)	0.03	1.07 (0.99, 1.16)	0.09	0.97
Itchy flexural rash in last 12 months	1.06 (1.02, 1.10)	0.003	1.05 (1.02, 1.08)	0.002	0.71
Severe itchy flexural rash	1.11 (1.04, 1.19)	0.003	1.19 (1.11, 1.28)	< 0.0001	0.13

\*Relevant disease label: asthma ever (for wheeze symptoms), hay fever ever (for rhinitis symptoms), eczema ever (for itchy rash symptoms).

Table 5. Association of symptoms and disease labels with total and older siblings, before and after adjustment for covariates

Symptom (6 to 7-year-olds)	Total siblings (odds ratio per additional sibling) All children as in Table 1		Total siblings (odds ratio per additional sibling) Before adjustment, in children with covariate data		Total siblings (odds ratio per additional sibling) After adjustment, in children with covariate data	
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value
Wheeze ever	0.96 (0.94, 0.98)	< 0.0001	0.96 (0.94, 0.98)	< 0.0001	0.96 (0.94, 0.98)	< 0.0001
Wheeze in last 12 months	0.99 (0.97, 1.01)	0.35	0.99 (0.97, 1.02)	0.56	0.99 (0.96, 1.01)	0.19
Severe wheeze in last 12 months	1.06 (1.03, 1.09)	< 0.0001	1.06 (1.02, 1.09)	0.0007	1.03 (1.00, 1.06)	0.07
Asthma ever	0.98 (0.96, 1.00)	0.11	0.99 (0.96, 1.01)	0.22	0.98 (0.96, 1.01)	0.12
Rhinitis ever	0.94 (0.93, 0.96)	< 0.0001	0.94 (0.93, 0.96)	< 0.0001	0.94 (0.93, 0.96)	< 0.0001
Rhinoconjunctivitis in last 12 months	0.98 (0.96, 1.00)	0.09	0.99 (0.97, 1.01)	0.37	0.99 (0.97, 1.01)	0.36
Severe rhinoconjunctivitis	1.04 (0.97, 1.11)	0.31	1.05 (0.97, 1.13)	0.21	1.03 (0.95, 1.11)	0.48
Hay fever ever	0.92 (0.90, 0.95)	< 0.0001	0.92 (0.89, 0.94)	< 0.0001	0.92 (0.90, 0.95)	< 0.0001
Itchy rash ever	1.00 (0.98, 1.02)	0.81	1.00 (0.98, 1.02)	0.67	1.00 (0.98, 1.02)	0.81
Itchy flexural rash in last 12 months	1.00 (0.98, 1.02)	0.91	1.00 (0.98, 1.03)	0.72	1.01 (0.98, 1.03)	0.59
Severe itchy flexural rash	1.18 (1.11, 1.24)	< 0.0001	1.18 (1.11, 1.26)	< 0.0001	1.13 (1.05, 1.20)	0.0004
Eczema ever	0.93 (0.91, 0.95)	< 0.0001	0.93 (0.91, 0.95)	< 0.0001	0.95 (0.93, 0.97)	< 0.0001

  

Symptom (6 to 7-year-olds)	Older siblings (adjusted for younger siblings) All children as in Table 2		Older siblings (adjusted for younger siblings) Before adjustment, in children with covariate data		Older siblings (adjusted for younger siblings) After adjustment, in children with covariate data	
	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value	OR (95% CL)	<i>P</i> value
Wheeze ever	0.97 (0.95, 0.98)	< 0.0001	0.97 (0.95, 0.99)	0.002	0.98 (0.96, 1.00)	0.04
Wheeze in last 12 months	1.01 (0.99, 1.03)	0.38	1.01 (0.99, 1.04)	0.43	1.01 (0.98, 1.04)	0.45
Severe wheeze in last 12 months	1.07 (1.04, 1.10)	< 0.0001	1.06 (1.03, 1.10)	0.0009	1.05 (1.01, 1.09)	0.02
Asthma ever	0.99 (0.97, 1.01)	0.27	0.99 (0.96, 1.02)	0.52	1.00 (0.97, 1.03)	0.82
Rhinitis ever	0.93 (0.91, 0.94)	< 0.0001	0.93 (0.91, 0.95)	< 0.0001	0.93 (0.91, 0.95)	< 0.0001
Rhinoconjunctivitis in last 12 months	0.98 (0.96, 1.00)	0.03	0.98 (0.96, 1.01)	0.25	0.99 (0.97, 1.02)	0.69
Severe rhinoconjunctivitis	1.00 (0.93, 1.07)	0.89	1.00 (0.91, 1.09)	0.92	1.01 (0.92, 1.10)	0.90
Hay fever ever	0.91 (0.89, 0.93)	< 0.0001	0.90 (0.87, 0.93)	< 0.0001	0.91 (0.88, 0.94)	< 0.0001
Itchy rash ever	0.98 (0.96, 1.00)	0.23	0.97 (0.95, 0.99)	0.01	0.97 (0.95, 1.00)	0.03
Itchy flexural rash in last 12 months	0.98 (0.96, 1.00)	0.09	0.98 (0.96, 1.01)	0.19	0.98 (0.95, 1.01)	0.24
Severe itchy flexural rash	1.14 (1.08, 1.20)	< 0.0001	1.14 (1.06, 1.22)	0.0004	1.09 (1.01, 1.18)	0.03
Eczema ever	0.90 (0.88, 0.92)	< 0.0001	0.90 (0.88, 0.92)	< 0.0001	0.92 (0.90, 0.94)	< 0.0001

All analyses are adjusted for sex, region, language and national GNI per capita. Additional covariates for the total siblings analysis: gender, maternal education, parental smoking, cat, dog, truck traffic and cooking fuels (all at age 6–7). Additional covariates for the older siblings analysis: gender, maternal education, mother smoking in the first year of life, cat, dog and farm animal exposure in the first year, birthweight, breast-feeding, paracetamol use in the first year, antibiotic use in the first year.

speech-limiting wheeze in the last 12 months was 1.12 (95% CI 1.07–1.17) in the younger children, and 1.10 (1.07–1.13) in the older age group. Also, the per-sibling odds ratios for itchy rash which did not clear during the last 12 months were 1.09 (1.06–1.12) at age 6–7 and 1.08 (1.05–1.11) among adolescents. Thus, the significant associations with more severe disease shown in Table 3 are not solely attributable to the sleep disturbance dimension.

Disease labels have not been a prominent feature of previous ISAAC reports due to concerns about differential use of clinical terms in different countries or cultures. Here, however, the disease labels 'hay fever ever' and 'eczema ever' display a different epidemiology

to that of current symptoms. An interesting and novel feature of our analysis is the variation between countries with different levels of affluence in the protective effects of older siblings on hay fever ever and eczema ever. Most of the affluent countries, in which this effect is seen, lie outside the tropics, and the type of seasonal allergic rhinitis that is termed 'hay fever' may be mainly a phenomenon of temperate climates. Thus, confounding of affluence by latitude could be a contributing factor for the hay fever findings. On the other hand, use of the term 'eczema' is probably less prone to this type of climatic confounding and shows a similar pattern to hay fever in both age groups.



The 'hygiene hypothesis' for allergic disease was developed from observations on parental reports of 'hay fever' and 'eczema' among their offspring in two British birth cohorts [2]. More recent commentaries have suggested not only that the immunological processes underlying sibship size effects may extend to a wider range of disease conditions [33–35], but also that mechanisms other than reduced exposure to infection may need to be considered as explanations for the associations of asthma and allergies with family size and birth order, even in higher-income countries [35–38].

The global perspective provided by ISAAC suggests a more complex picture, with variations between less affluent and more affluent countries, both in the immunology of asthma, rhinoconjunctivitis and eczema in children, and in their epidemiological determinants. In ISAAC Phase Two, atopy (as measured by aeroallergen skin prick tests) was less strongly associated with symptoms of asthma [39], rhinoconjunctivitis [30] and eczema [40] in centres from lower-income countries, than in centres from countries with higher GNI per capita.

The present analysis of ISAAC Phase Three demonstrates that the inverse association of sibship size with these 'allergic' diseases is largely confined to higher-income countries, plausibly because the contribution of atopic mechanisms to asthma, rhinoconjunctivitis and eczema is much greater in affluent populations. In contrast, the new observations of greater symptom severity among children from larger families seem to be a more consistent phenomenon worldwide and deserve further exploration and explanation.

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## Acknowledgements

We are grateful to the children and parents who participated in ISAAC Phase Three, and the coordination and assistance by the school staff is sincerely appreciated. The authors also acknowledge and thank the many funding bodies throughout the world that supported the individual ISAAC centres and collaborators and their meetings. Without help from all of the above, ISAAC would not have been such a global success.

## Funding

Many New Zealand funding bodies have contributed support for the ISAAC International Data Centre (IIDC) during the periods of fieldwork and data compilation (the Auckland Medical Research Foundation, the Health Research Council of New Zealand, the Asthma and Respiratory Foundation of New Zealand, the Child Health Research Foundation, the Hawke's Bay Medical Research Foundation, the Waikato Medical Research Foundation, Glaxo Wellcome New Zealand, the NZ Lottery Board and Astra Zeneca New Zealand). Glaxo Wellcome International Medical Affairs supported the regional coordination for Phase Three and the IIDC. The BUPA Foundation was the main source of funding for the IIDC during the period of statistical analyses reported in this paper.

## Conflict of interest

The authors declare no conflict of interest.

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## Appendix 1: ISAAC Phase Three Study Group

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