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Comparison of individual-level and population-level risk factors for rhinoconjunctivitis, asthma, and eczema in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three

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ABSTRACT

Background: Symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in children cluster at both the individual and population levels.

Objectives: To assess individual-level and school-level risk factors for symptoms of rhinoconjunctivitis and compare them to corresponding associations with symptoms of asthma and eczema in Phase Three of the International Study of Asthma and Allergies in Childhood.

Methods: We studied 116,863 children aged 6–7 years from 2163 schools in 59 centres and 22 countries and 224,436 adolescents aged 13–14 years from 2037 schools in 97 centres in 41 countries. Multilevel logistic regression models were fitted with random intercepts for school, centre, and country, adjusting for sex and maternal education at the child level. Associations between symptoms and a range of lifestyle and environmental risk factors were assessed for both the child's exposure and mean exposure at the school. Models were fitted for rhinoconjunctivitis, asthma, and eczema singly (unimorbidity) and for combinations of these conditions (multimorbidity).

Results: Generally, associations between symptoms and exposures at the school level were similar in direction and magnitude to those at the child level. Associations with multimorbidity were stronger than for unimorbidity, particularly in individuals with symptoms of all three diseases, but risk factor associations found in conventional single disease analyses persisted among children with only one condition, after excluding multimorbid groups.
Comparisons of individuals with only one disease showed that many risk factor associations were consistent across the three conditions. More strongly associated with asthma were low birthweight, cat exposure in infancy, and current maternal smoking. Current paracetamol use was more

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[1] The ISAAC Phase Three Study Group are listed in the Appendix section. Full list of author information is available at the end of the article

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strongly associated with asthma and rhinoconjunctivitis than eczema. Breastfeeding was more strongly associated with eczema than asthma or rhinoconjunctivitis.
The direction and magnitude of most risk factor associations were similar in affluent and non-affluent countries, although notable exceptions include farm animal contact in infancy and larger sibships, which were associated with increased risk of rhinoconjunctivitis in non-affluent countries but reduced risk in affluent countries. In both age groups, current paracetamol use increased risk of each disease to a greater extent in affluent countries than in non-affluent countries. Effects of paracetamol and antibiotics in infancy were more consistent between richer and poorer settings.

Conclusions: Most of the environmental and lifestyle correlates of rhinoconjunctivitis, asthma and eczema in childhood display similarity across the three conditions, even in less affluent settings where allergic sensitisation is less likely to explain the concordant epidemiological patterns.

Trial registration: Not applicable.

Keywords: Rhinoconjunctivitis, Asthma, Eczema, Multimorbidity, Global

INTRODUCTION

The International Study of Asthma and Allergies in Childhood (ISAAC) has used standardised questionnaires to assess prevalence, time trends, and epidemiological associations for symptoms of non-infective rhinoconjunctivitis, asthma, and eczema among children from over 300 centres in more than 100 countries worldwide.[1,2] More detailed biomedical assessment in 30 diverse centres in ISAAC Phase Two[3-5] has demonstrated that allergic sensitisation accounts for a much lower proportion of rhinoconjunctivitis, asthma, and eczema symptoms in centres from low- and middle-income countries than it does in more affluent settings which feature more prominently in the epidemiological literature.

Previous publications from ISAAC Phase Three have presented the associations of each of the 3 diseases with single environmental or lifestyle factors.[6-19] More recently, these have been summarised across multiple risk factors for symptoms of asthma[20] and eczema,[21] and comparisons have been made between the relationship of each of these diseases to exposures measured at the level of individuals and exposures averaged at the area level (schools).

In this paper, we apply the multi-level analytical approach to symptoms of rhinoconjunctivitis and extend our overview to assess similarities and differences in the epidemiological patterns of the 3 diseases, singly and in combination. We also compare these patterns between centres from higher-income and lower-income countries.

METHODS

Study design

A brief summary of the ISAAC Phase Three methods are presented in this paper and more details are available elsewhere.[1] ISAAC Phase Three was a multi-centre, multi-country, cross-sectional study of children (age 6–7 years) and adolescents (age 13–14 years). Within a defined geographical area (centre), a sample of schools were chosen at random. All children within the age groups in those schools were asked to participate.[1] The Phase Three survey took place in 2000–2003 and included two standardised questionnaires (http://isaac.auckland.ac.nz); the original symptom questionnaire from ISAAC Phase One[1,2] with information on symptoms of asthma, eczema and rhinoconjunctivitis, and an environmental questionnaire which collected data on a range of possible risk factors for the development of these disorders.[1]

Variable definitions

The 3 main outcomes of interest, asthma, eczema, and rhinoconjunctivitis, are defined using

previous ISAAC conventions.[1–3] These 3 diseases are likely to be undiagnosed in many cases as people seek to self-treat (particularly rhinoconjunctivitis), and the rate of doctor diagnoses is likely to vary widely from country to country. Thus, outcomes assessed in the ISAAC questionnaire are based on a description of symptoms rather than a diagnosis of disease.

Rhinoconjunctivitis is defined by positive responses to all of the following 3 questions:

Have you [has your child] ever had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?

In the past 12 months, have you [has your child] had a problem with sneezing, or a runny, or blocked nose when you [he/she] did not have a cold or the flu?

In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

Eczema is defined by positive responses to all of the following 3 questions:

Have you [has your child] ever had an itchy rash which was coming and going for at least six months?

Have you [has your child] had this itchy rash at any time in the past 12 months?

Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

Asthma is defined by a positive response to the following question:

Have you [has your child] had wheezing or whistling in the chest in the past 12 months?

The environmental questionnaire for the 6-7-year-old age group contained more questions on early life exposures as this was completed by the parents of the child. We restricted our analyses to the risk factors which had shown associations with either rhinoconjunctivitis, asthma, or eczema symptoms in the last 12 months in previous analyses at the individual level. Variables included for the younger age group (6–7 years) were paracetamol use in the first year of life and in the past 12 months,[6] antibiotic use in the first year of life,[7] breast feeding,[8] pets in the home in the first year of life,[9] regular contact with farm animals in the first year of life, and prenatally through maternal contact,[10] truck traffic in the last 12 months,[11] fast food consumption in the last 12 months,[12] television viewing in the last 12 months,[13] parental smoking in the last 12 months,[14] open fire cooking,[15] birth weight,[16] and number of siblings.[17] For the older age group (13–14 years), truck traffic,[11] fast food consumption,[12] television viewing,[13] parental smoking,[14] and paracetamol use,[18] all in the past 12 months, open fire cooking[15] and number of siblings[17] were included.

Most of the above risk factors were parameterised as binary variables from "yes/no" questions in the environmental questionnaire. The exceptions were: paracetamol use in the past 12 months (at least once per month vs. less than once per month), heavy truck traffic (frequently or almost the whole day vs. seldom or never), fast food consumption (once per week or more vs. less than once per week), television viewing (at least 1 h per day vs. less than 1 h per day), birth weight (less than 2.5 kg vs. at least 2.5 kg), and number of siblings (2 or more siblings vs. 1 or no siblings). Full definitions are in Table S1, Supporting Material. The highest level of maternal education was recorded as primary, secondary, tertiary or missing/not stated.

Gross National Income (GNI) in 2002 was obtained from the World Bank website[22] where available, with gaps filled by the CIA World Factbook.[23] Countries were classified as 'affluent' or 'non-affluent' using a 2001 GNI value of US$9205 per capita as a cut-off, which separates high-income countries from low and middle-income countries.[24]

Statistical analyses

Separate analyses were conducted for the 2 age groups. Centres with fewer than 1000 individuals in an age group were excluded from the analyses

for that age group. Each school was required to have at least 10 individuals to be included in the analyses for that age group. In addition, a response rate of at least 60% was required for children and at least 70% for adolescents for a centre to be included.

Mixed effect (multilevel) logistic regression models were used for all analyses with random intercepts at the 3 highest levels of the four-level hierarchy: individuals, schools, centres and countries (from lowest to highest). All analyses additionally adjusted for sex and maternal education as confounders at the individual level.

The potential risk factors for rhinoconjunctivitis symptoms were compared at individual level and at school level in a similar way to previous publications on asthma[20] and eczema.[21] The school-level risk factors are less prone to reverse causation bias than the individual-level risk factors as a change in behaviour of a few people with the disease will not greatly affect the school-level prevalence of that risk factor. Thus, similar results at both levels can be interpreted as suggestive evidence against reverse causation influencing individual-level associations.

For comparison of risk factor associations between the 3 different diseases, 3 different modelling approaches were used:

i) Standard outcomes - modelling the 3 disease outcomes separately but within the same sample of children,

ii) Multimorbid outcomes - modelling each of the different combination of disease outcomes (i.e. asthma only, eczema only, rhinoconjunctivitis only, asthma and eczema, asthma and rhinoconjunctivitis, eczema and rhinoconjunctivitis, and all 3) against those with no disease and comparing the resulting risk factor associations, and

iii) Unimorbid outcomes - comparing individuals with only asthma, only eczema or only rhinoconjunctivitis symptoms in the last 12 months and modelling the 3 combinations of disease pairs to evaluate if the risk factors are more associated with one disease than another.

In each of these modelling analyses we checked for collinearity between the risk factors by comparing the standard errors in the fully adjusted model (all risk factors and confounders) to those in minimally adjusted models (only the risk factor of interest and the confounders).

Additionally, we ran each model separately for "affluent" and "non-affluent" countries (with the exception of the multimorbid outcomes analyses where some of the sample sizes were too small). We also tested for an interaction between country affluence and each risk factor individually. Analyses were conducted using Stata version 15.[25]

RESULTS

Derivation and characteristics of the sample analysed

In the age 6–7 analyses there were 75 centres (comprising 221,280 children) that met the standard ISAAC inclusion criteria[1] of a minimum of 1000 children and a response rate of at least 60%. For multi-level analysis, 263 schools (1427 children in total) were excluded due to having fewer than 10 children and a further 102,990 children excluded for not having data available for all 3 outcomes (asthma, eczema, and rhinoconjunctivitis symptoms), confounders (sex and mother's level of education), and all the included risk factors. The remaining 116,863 children, on which these results are based (the "synthesis sample"), were from 2163 schools within 59 centres, in 22 different countries (Fig. S1, Supporting Material).

The prevalence of rhinoconjunctivitis symptoms among the 6-7-year-olds included in this analysis was 8.9%, asthma symptoms was 9.7%, and eczema symptoms was 7.3%. The overall prevalence of the exposures ranged from 1.8% for current open fire cooking to 80.5% for ever breastfed. These and further summary statistics for the synthesis sample are presented in Table 1.

For the 13-14 year-olds there were 122 centres (comprising 362,048 adolescents) meeting the ISAAC criteria[1] of a minimum of 1000 per centre and a response rate of at least 70%. For multi-level analysis, 64 schools (comprising 298 individuals) were excluded due to having fewer than 10 adolescents. A further 137,314 individuals were excluded for not having data available for all three outcomes (asthma, eczema and rhinoconjunctivitis

Type	Variable	Age 6-7 years (n = 116,863)						Age 13-14 years (n = 224,436)					
		Individual-level prevalence	Centre-level prevalence (%) quartiles					Individual-level Prevalence	Centre-level prevalence (%) quartiles				
		(%)	Min	Q1	Med	Q3	Max	(%)	Min	Q1	Med	Q3	Max
Outcome	Rhinoconjunctivitis in the past 12 months	8.9	0.9	3.7	7.5	12.2	25.2	14.1	1.2	8.8	13.2	18.5	31.7
	Asthma symptoms in the past 12 months	9.7	2.5	5.4	9.0	13.2	29.7	10.6	0.7	6.1	9.8	14.4	32.4
	Eczema symptoms in the past 12 months	7.3	0.6	2.5	6.0	10.9	18.9	6.2	0.1	3.0	4.7	8.0	23.8
Multiple													
outcome	No symptoms	80.1	62.2	74.1	80.1	89.0	95.0	76.0	51.8	69.6	75.8	83.5	98.2
	Rhinoconjunctivitis only	4.7	0.3	2.2	3.6	5.2	16.5	8.8	1.1	5.0	8.4	11.1	22.4
	Asthma only	5.8	1.7	3.6	5.0	7.4	26.1	6.1	0.6	3.7	5.5	8.0	19.6
	Eczema only	4.4	0.6	1.8	3.2	5.5	11.4	3.2	0.0	1.6	2.5	4.1	13.4
	Rhinoconjunctivitis and Asthma	2.1	0.2	0.8	2.0	3.3	4.9	2.9	0.0	1.4	2.6	4.0	10.3
	Rhinoconjunctivitis and Eczema	1.1	0.0	0.3	0.8	1.6	4.3	1.4	0.0	0.5	0.9	1.6	8.0
	Asthma and Eczema	0.9	0.0	0.3	0.6	1.3	3.9	0.7	0.0	0.2	0.5	1.0	2.9
	Symptoms of all three	0.9	0.0	0.2	0.8	1.4	3.3	0.9	0.0	0.3	0.8	1.2	4.1
Early life													
exposure	Low birthweight	7.7	0.0	5.2	6.2	9.4	39.4	NA	NA	NA	NA	NA	NA
	Breastfed ever	80.5	29.2	79.3	84.7	91.2	97.0	NA	NA	NA	NA	NA	NA

(continued)

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Type	Variable	Age 6-7 years (n = 116,863)						Age 13-14 years (n = 224,436)					
		Individual-level prevalence	Centre-level prevalence (%) quartiles					Individual-level Prevalence	Centre-level prevalence (%) quartiles				
		(%)	Min	Q1	Med	Q3	Max	(%)	Min	Q1	Med	Q3	Max
	Farm animals (prenatal)	7.7	0.7	4.5	7.5	10.7	24.2	NA	NA	NA	NA	NA	NA
	Farm animals (1st year)	9.3	1.9	6.2	9.3	13.5	24.9	NA	NA	NA	NA	NA	NA
	Cat (1st year)	10.9	1.2	4.9	8.3	11.9	53.8	NA	NA	NA	NA	NA	NA
	Dog (1st year)	19.8	0.7	10.6	18.2	27.6	46.3	NA	NA	NA	NA	NA	NA
	Paracetamol (1st year)	66.1	8.6	59.0	68.1	82.7	93.9	NA	NA	NA	NA	NA	NA
	Antibiotics (1st year)	55.6	18.8	52.0	57.8	62.3	77.7	NA	NA	NA	NA	NA	NA
Current													
exposure	2 or more siblings	34.7	12.4	21.9	31.8	45.3	83.1	53.9	3.9	37.9	57.6	73.3	100.0
	Heavy truck traffic (past 12 months)	37.9	6.3	32.1	37.8	43.8	67.4	39.5	15.2	32.3	38.0	45.0	90.9
	Fast food (past 12 months)	39.6	9.3	20.4	42.4	54.3	98.1	53.6	6.1	42.7	53.7	66.4	98.3
	Television (past 12 months)	80.1	40.1	72.9	82.2	89.1	95.3	85.7	42.9	80.9	90.0	93.2	98.0
	Paternal tobacco (past 12 months)	31.7	3.2	19.9	28.9	43.6	55.3	38.5	2.7	23.9	36.4	46.4	94.1
	Maternal tobacco (past 12 months)	16.3	0.0	1.6	12.6	24.5	46.6	18.3	0.4	2.7	14.1	28.9	93.7
	Paracetamol (past 12 months)	17.8	0.0	9.9	15.7	23.9	65.3	26.7	0.0	18.4	28.6	34.7	66.0
	Open fire cooking	1.8	0.0	0.3	1.1	2.0	44.8	5.2	0.0	0.6	1.3	4.1	86.1

Table 1. (Continued) Summary statistics for variables and their prevalence in subjects who had data present for the 3 outcomes, the confounders sex and maternal education level and all other exposures of interest in the table (the "synthesis sample")

symptoms), confounders (sex and mother's level of education) and all the included risk factors of interest. The remaining "synthesis sample" contained 224,436 adolescents from 2037 schools within 97 centres, in 41 different countries (Fig. S2, Supporting Material).

The prevalence of rhinoconjunctivitis symptoms among the 13-14-year-olds included in this analysis was 14.1%, asthma symptoms was 10.6%, and eczema symptoms was 6.2%. The overall prevalence of the exposures ranged from 5.2% for current open fire cooking to 85.7% for watching television at least an hour a day. For further details, see Table 1.

Multi-level models for rhinoconjunctivitis

Table 2 presents associations at the individual level (within schools) and the area level (between schools, within centre) for exposures of interest, adjusted for sex and mother's educational level ("minimally adjusted"), and for each other ("fully adjusted"), as derived from the multi-level model.

For the 6–7 age group, the strongest mutually adjusted associations with rhinoconjunctivitis at the individual level were current paracetamol use (odds ratio = 2.02; 95% CI = 1.92–2.13) and antibiotics in the first year (1.58; 1.51–1.66). These associations were very similar at the school level with odds ratios 2.04 (1.43–2.89) and 1.39 (1.03–1.88) respectively. However, the weaker child-level association with early paracetamol use (1.39; 1.32–1.47) was not seen at the school level (0.99; 0.73–1.35). Similarly, a modest child-level association with heavy truck traffic (1.17; 1.12–1.22) was inconsistent with the inverse relationship at school level (odds ratio 0.92; 0.73–1.16). Low birthweight showed no evidence of an association with rhinoconjunctivitis at the individual level (1.04; 0.96–1.13), but at the school level the association was strong and significant (2.59; 1.56–4.29). Similarly, a school-level association was evident for television viewing (1.45; 1.05–2.01) but not for children within schools (0.93; 0.88–0.98).

In the 13–14 age group, there was a strong association at the individual level with current paracetamol use (1.76; 1.71–1.81) which was even stronger at the school-level (3.48; 2.66–4.56). A less strong child-level association was observed for heavy truck traffic (1.23; 1.20–1.26), which was consistent at the school level (1.16; 0.94–1.44) though there was less precision on the latter estimate. Paternal and maternal smoking had similar effects at the individual-level, but at the school level their associations were in opposite directions. For cooking by open fire, the school-level association (2.02; 1.39–2.93) was much stronger than the child-level association (1.16; 1.08–1.26).

The precision of estimates from the fully adjusted models and those from the corresponding minimally adjusted models (Table 2) were compared and no evidence of collinearity was found.

Comparison of risk factor patterns for rhinoconjunctivitis, asthma and eczema

Table 3 compares, by age group, the individual-level associations of each exposure with symptoms of rhinoconjunctivitis (from Table 2), asthma, and eczema (previously published in slightly different samples[20,21] but reanalysed here on the same "synthesis sample" as for rhinoconjunctivitis).

For younger children, the strongest associations in the fully adjusted analyses were similar across all 3 outcomes. They were: current paracetamol use (ORs for rhinoconjunctivitis symptoms 2.02; asthma symptoms 2.07; and eczema symptoms 1.46), antibiotic use in the first year of life (1.58; 1.66; 1.40, respectively), and paracetamol use in the first year of life (1.39; 1.34; 1.29). Heavy truck traffic showed a less strong but consistent association with all 3 outcomes (1.17; 1.19; 1.12). Similarly, cat ownership in the first year of life had a consistent direction of association, somewhat stronger with asthma (1.22) than with rhinoconjunctivitis (1.09) and eczema (1.10).

The 3 diseases differed in their associations with some other risk factors. Exposures showing a harmful association with asthma but no statistically significant association with rhinoconjunctivitis and eczema were cooking on an open fire and fast food. Low birthweight showed a harmful association with asthma (OR = 1.15), a marginally statistically significant protective effect with eczema (OR = 0.90), and no association with rhinoconjunctivitis. Breast feeding was associated with increased risk of eczema (1.11), a marginally statistically significant protective association with

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Age group	Exposures of interest	Minimally adjusted model[b]		Fully adjusted model[c]	
		Individual-level OR (95% CI)	School-level OR (95% CI)	Individual-level OR (95% CI)	School-level OR (95% CI)
6–7 years (n = 116,863)	Low birthweight	1.11 (1.02, 1.20)	3.03 (1.88, 4.88)	1.04 (0.96, 1.13)	2.59 (1.56, 4.29)
	Breastfed ever	0.97 (0.92, 1.02)	0.52 (0.37, 0.73)	1.00 (0.95, 1.06)	0.62 (0.44, 0.88)
	Farm animals (prenatal)	1.36 (1.27, 1.46)	1.56 (1.10, 2.22)	1.18 (1.07, 1.30)	1.16 (0.61, 2.20)
	Farm animals (1st year)	1.30 (1.21, 1.39)	1.55 (1.11, 2.16)	1.07 (0.98, 1.17)	1.19 (0.65, 2.18)
	Cat (1st year)	1.19 (1.11, 1.27)	1.36 (0.94, 1.97)	1.09 (1.01, 1.16)	1.10 (0.72, 1.68)
	Dog (1st year)	1.16 (1.10, 1.21)	1.21 (0.89, 1.63)	1.07 (1.01, 1.12)	0.94 (0.67, 1.31)
	Paracetamol (1st year)	1.80 (1.71, 1.89)	1.32 (1.01, 1.75)	1.39 (1.32, 1.47)	0.99 (0.73, 1.35)
	Antibiotics (1st year)	1.84 (1.75, 1.92)	1.45 (1.09, 1.91)	1.58 (1.51, 1.66)	1.39 (1.03, 1.88)
	2 or more siblings	0.99 (0.95, 1.04)	1.04 (0.83, 1.30)	0.98 (0.94, 1.03)	0.88 (0.69, 1.12)
	Heavy truck traffic (current)	1.25 (1.20, 1.31)	1.12 (0.90, 1.40)	1.17 (1.12, 1.22)	0.92 (0.73, 1.16)
	Fast food (current)	1.04 (0.99, 1.09)	1.13 (0.89, 1.42)	0.99 (0.94, 1.03)	1.04 (0.82, 1.32)
	Television (current)	0.98 (0.92, 1.03)	1.59 (1.18, 2.14)	0.93 (0.88, 0.98)	1.45 (1.05, 2.01)
	Paternal tobacco (current)	1.11 (1.06, 1.16)	1.34 (1.03, 1.74)	1.07 (1.02, 1.12)	0.86 (0.63, 1.19)
	Maternal tobacco (current)	1.12 (1.06, 1.19)	1.67 (1.25, 2.23)	1.05 (0.99, 1.11)	1.39 (0.98, 1.96)
	Paracetamol (current)	2.30 (2.18, 2.42)	2.30 (1.66, 3.20)	2.02 (1.92, 2.13)	2.04 (1.43, 2.89)
	Open fire cooking (current)	1.03 (0.86, 1.23)	2.21 (1.16, 4.22)	0.99 (0.82, 1.19)	1.85 (0.92, 3.71)

(continued)

Age group	Exposures of interest	Minimally adjusted model[b]		Fully adjusted model[c]	
		Individual-level OR (95% CI)	School-level OR (95% CI)	Individual-level OR (95% CI)	School-level OR (95% CI)
13–14 years (n = 224,436)	2 or more siblings	1.05 (1.02, 1.08)	1.02 (0.83, 1.25)	1.04 (1.01, 1.07)	0.93 (0.75, 1.15)
	Heavy truck traffic (current)	1.27 (1.24, 1.30)	1.35 (1.09, 1.67)	1.23 (1.20, 1.26)	1.16 (0.94, 1.44)
	Fast food (current)	1.10 (1.07, 1.13)	1.31 (1.07, 1.61)	1.06 (1.03, 1.08)	1.24 (1.02, 1.51)
	Television (current)	1.04 (1.00, 1.08)	1.35 (0.97, 1.88)	1.01 (0.97, 1.05)	1.20 (0.86, 1.68)
	Paternal tobacco (current)	1.16 (1.13, 1.19)	1.08 (0.84, 1.40)	1.10 (1.07, 1.13)	0.75 (0.55, 1.00)
	Maternal tobacco (current)	1.21 (1.17, 1.25)	1.46 (1.08, 1.97)	1.14 (1.10, 1.17)	1.56 (1.12, 2.18)
	Paracetamol (current)	1.80 (1.75, 1.85)	3.52 (2.69, 4.60)	1.76 (1.71, 1.81)	3.48 (2.66, 4.56)
	Open fire cooking (current)	1.16 (1.08, 1.25)	1.73 (1.19, 2.49)	1.16 (1.08, 1.26)	2.02 (1.39, 2.93)

Table 2. (Continued) Individual-level (within school) and school-level (between school) effects of exposures on rhinoconjunctivitis symptoms using the synthesis sample[a]. Mixed logistic regression models with random intercepts at the school, centre and country levels. *a. Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest. b. Adjusted for sex and mothers level of education. c. Adjusted for sex, mothers level of education and all other variables in the table (within age group)*

asthma (OR = 0.95) and no association with rhinoconjunctivitis.

Among adolescents, exposures showing consistent associations with all 3 diseases were current paracetamol use (odds ratios for rhinoconjunctivitis 1.76; asthma 1.80; and eczema 1.58), heavy truck traffic (1.23; 1.20; 1.31, respectively), cooking on an open fire (1.16; 1.19; 1.49), mother smoking (1.14; 1.22; 1.11), and father smoking (1.10; 1.11; 1.15). Weaker associations with fast food were also consistent (1.06; 1.07; 1.06) across the 3 diseases (Table 3).

Comparison of risk factor patterns in affluent and less affluent countries

Fig. 1A–C summarise the risk factor-disease associations by age group, stratified by national per capita GNI (Numerical results are shown in Table S2, Supporting Material.). Many of the risk factor-disease associations are fairly consistent between affluent and non-affluent settings, with most differences being within the range expected by chance (interaction $p > 0.01$). In the section below we focus upon the most significant inconsistencies (interaction $p < 0.0001$ for one or more diseases).

For rhinoconjunctivitis among 6-7-year-olds (Fig. 1A and B), notable differences by national per capita GNI are increased risk in non-affluent countries with farm animal contact in infancy (1.19; 1.07–1.33) and having more than two siblings (1.06; 1.00–1.13), whereas in affluent countries, these associations are protective (0.88; 0.75–1.03 and 0.87; 0.81–0.94, respectively).

For asthma among 6-7-year-olds (Fig. 1A and B), farm animal exposure in pregnancy showed a

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Age group	Exposures of interest	Fully adjusted model[a]		
		Rhinoconjunctivitis symptoms OR (95% CI)	Asthma symptoms OR (95% CI)	Eczema symptoms OR (95% CI)
6–7 years (n = 116,863)	Low birthweight	1.04 (0.96, 1.13)	1.15 (1.07, 1.25)	0.90 (0.82, 0.99)
	Breastfed ever	1.00 (0.95, 1.06)	0.95 (0.90, 1.00)	1.11 (1.04, 1.17)
	Farm animals (prenatal)	1.18 (1.07, 1.30)	1.19 (1.08, 1.30)	1.12 (1.01, 1.24)
	Farm animals (1st year)	1.07 (0.98, 1.17)	0.98 (0.89, 1.06)	1.13 (1.03, 1.25)
	Cat (1st year)	1.09 (1.01, 1.16)	1.22 (1.14, 1.30)	1.10 (1.02, 1.18)
	Dog (1st year)	1.07 (1.01, 1.12)	1.03 (0.98, 1.08)	1.06 (1.00, 1.12)
	Paracetamol (1st year)	1.39 (1.32, 1.47)	1.34 (1.27, 1.41)	1.29 (1.22, 1.37)
	Antibiotics (1st year)	1.58 (1.51, 1.66)	1.66 (1.59, 1.74)	1.40 (1.33, 1.47)
	2 or more siblings	0.98 (0.94, 1.03)	0.97 (0.92, 1.01)	0.94 (0.90, 0.99)
	Heavy truck traffic (current)	1.17 (1.12, 1.22)	1.19 (1.14, 1.24)	1.12 (1.06, 1.17)
	Fast food (current)	0.99 (0.94, 1.03)	1.08 (1.04, 1.13)	0.99 (0.94, 1.05)
	Television (current)	0.93 (0.88, 0.98)	1.05 (0.99, 1.11)	0.96 (0.90, 1.02)
	Paternal tobacco (current)	1.07 (1.02, 1.12)	1.10 (1.05, 1.16)	1.04 (0.99, 1.10)
	Maternal tobacco (current)	1.05 (0.99, 1.11)	1.20 (1.14, 1.27)	1.05 (0.99, 1.12)
	Paracetamol (current)	2.02 (1.92, 2.13)	2.07 (1.97, 2.17)	1.46 (1.38, 1.55)
	Open fire cooking (current)	0.99 (0.82, 1.19)	1.21 (1.04, 1.42)	1.14 (0.96, 1.35)

(continued)

Age group	Exposures of interest	Fully adjusted model[a]		
		Rhinoconjunctivitis symptoms OR (95% CI)	Asthma symptoms OR (95% CI)	Eczema symptoms OR (95% CI)
13–14 years (n = 224,436)	2 or more siblings	1.04 (1.01, 1.07)	1.02 (0.99, 1.06)	1.08 (1.04, 1.12)
	Heavy truck traffic (current)	1.23 (1.20, 1.26)	1.20 (1.16, 1.23)	1.31 (1.26, 1.36)
	Fast food (current)	1.06 (1.03, 1.08)	1.07 (1.04, 1.10)	1.06 (1.02, 1.10)
	Television (current)	1.01 (0.97, 1.05)	1.02 (0.97, 1.07)	1.07 (1.01, 1.14)
	Paternal tobacco (current)	1.10 (1.07, 1.13)	1.11 (1.07, 1.14)	1.15 (1.11, 1.20)
	Maternal tobacco (current)	1.14 (1.10, 1.17)	1.22 (1.18, 1.27)	1.11 (1.06, 1.17)
	Paracetamol (current)	1.76 (1.71, 1.81)	1.80 (1.75, 1.86)	1.58 (1.52, 1.65)
	Open fire cooking (current)	1.16 (1.08, 1.26)	1.19 (1.10, 1.30)	1.49 (1.34, 1.65)

Table 3. (Continued) Single outcome models of fully adjusted[a], individual-level (within school) effects of exposures using the synthesis sample[b]. Mixed logistic regression models with random intercepts at the school, centre and country levels. *a. Adjusted for sex, mothers level of education and for all other variables in the table (within age group). b. Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest*

harmful association in non-affluent countries (1.32; 1.18–1.49) but no significant effect in affluent countries (0.98; 0.83–1.14). Breastfeeding ever showed a protective effect in non-affluent countries (0.87; 0.81–0.94) but no significant effect in affluent countries (1.02; 0.96–1.10). Cat exposure in infancy increased risk of asthma symptoms in both settings, but there was evidence of a stronger effect in non-affluent (1.36; 1.24–1.49) than affluent countries (1.10; 1.01–1.20). Conversely, current paracetamol use elevated asthma risk to a significantly greater extent in affluent (2.36; 2.19–2.56) than non-affluent settings (1.90; 1.78–2.02).

For eczema among 6-7-year-olds (Fig. 1A and B), early cat exposure was a risk factor in non-affluent countries (1.23; 1.11–1.36) but not in affluent countries (0.99; 0.90–1.09). Farm animal exposure in infancy increased eczema risk in non-affluent (1.25; 1.11–1.40) but not in affluent countries (0.95; 0.80–1.13), and a similar pattern was evident for farm animal exposure in pregnancy. Current paracetamol use was more strongly associated with eczema symptoms in affluent (1.65; 1.50–1.81) than non-affluent settings (1.35; 1.25–1.46), although this heterogeneity (interaction $p = 0.003$) was less significant than for asthma.

Stratifying the 13-14 year-old results in a similar manner (Fig. 1C and Table S2), few risk factors demonstrate differential effects in affluent and non-affluent countries. For rhinoconjunctivitis, open fire cooking increased risk in non-affluent countries (1.20; 1.11–1.30) but not in affluent countries (0.82; 0.62–1.07) (interaction $p = 0.008$). Across all 3 outcomes, current paracetamol use showed a harmful effect in both affluent and non-affluent countries, but the effect was stronger in affluent countries (interaction $p < 0.0001$ for rhinoconjunctivitis, $p = 0.0009$ for asthma, $p = 0.009$ for eczema).

Multimorbid (combinations of disease) models

In the 6-7 year-old synthesis sample, 80.1% of the children had no symptoms of any of the 3 outcomes. The proportion of children with only 1

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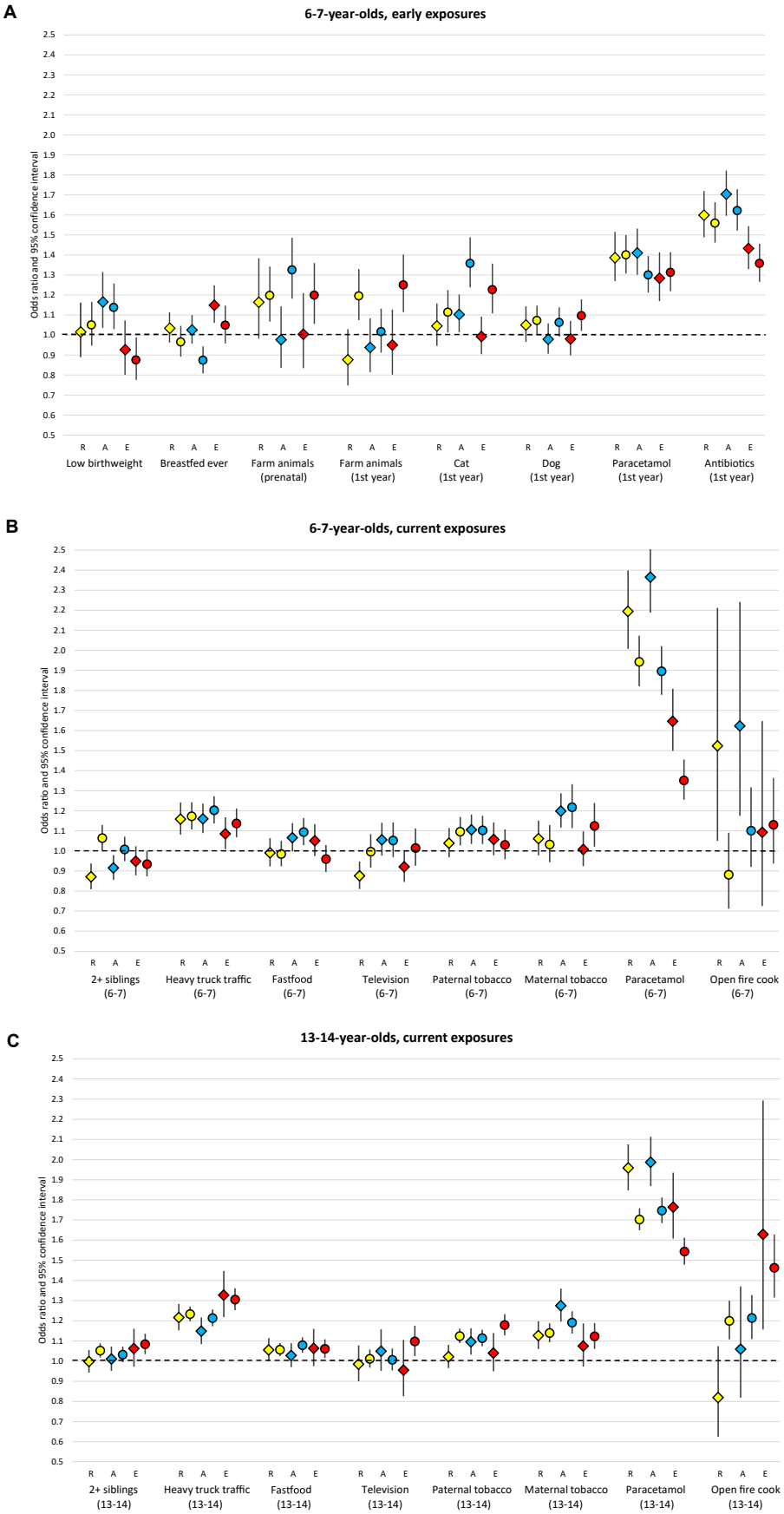

disease was 14.9% (rhinoconjunctivitis 4.7%, asthma 5.8%, eczema 4.4%). The proportions with 2 diseases was 4.1% (rhinoconjunctivitis and asthma 2.1%, rhinoconjunctivitis and eczema 1.1%, and asthma, and eczema 0.9%). Just 0.9% of the sample had symptoms of all 3 diseases (Table 1).

Using models comparing different combinations of disease outcomes to those with no disease (Table 4), we found that antibiotics in the first year of life showed a stronger effect among individuals with 2 or 3 diseases. Paracetamol in the first year had similar effects across any combination of the diseases, with a slightly stronger effect only noticed with individuals who have all 3 diseases. This was similar for current heavy truck traffic. Current paracetamol showed a stronger effect in asthma and rhinoconjunctivitis than eczema, as reflected in the combinations of multiple diseases with the strongest effects being in individuals with all 3 diseases or rhinoconjunctivitis and asthma (Table 4).

Among the 13-14 year-old synthesis sample, 76.0% had no symptoms of any of the 3 outcomes. The proportion of adolescents with only 1 disease was 18.1% (rhinoconjunctivitis 8.8%, asthma 6.1%, eczema 3.2%). A further 5.0% had symptoms of 2 of the diseases (rhinoconjunctivitis and asthma 2.9%, rhinoconjunctivitis and eczema 1.4% and asthma and eczema 0.7%). Only 0.9% had symptoms of all 3 diseases (Table 1).

Current paracetamol showed a stronger effect in individuals with more than one disease, with the strongest effect in those with all 3 diseases. Open fire cooking showed a stronger effect in all combinations that contain eczema (Table 4).

Importantly, in both age groups, risk factor associations with each disease in the whole population (Table 3) persisted among children with only 1 condition, after exclusion of multimorbid groups (Table 4).

Unimorbid (single disease case-only) models

Table 5 shows the results of 3 separate models, each comparing 2 of the unimorbid outcomes. Corresponding results, stratified by per capita GNI, are shown as Table S3 in the Supporting Material. Triangle plots appear as Figs. S3–S8 in the Supporting Material. An equilateral central triangle denotes a risk factor that has a similar strength of effect on all 3 diseases, the further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. In the plots the odds ratios displayed are all greater than or equal to one; they relate to whichever disease has the stronger effect (the corner they are closest to compared to the opposite corner).

In the 6-7 year-old age group, low birthweight was most strongly associated with asthma and more strongly associated with rhinoconjunctivitis than eczema. Early life antibiotic exposure showed a similar pattern but to a slightly reduced extent. Being breastfed ever showed a stronger association with eczema than both asthma and rhinoconjunctivitis. Owning a cat in the first year of life was most strongly associated with asthma but more strongly associated with eczema than rhinoconjunctivitis.

Some differences were evident between affluent and non-affluent countries (Table S3 and Fig. S6). Farm animal contact during pregnancy had effects in non-affluent countries which were more balanced between the diseases, but in affluent countries the effect was stronger on eczema and rhinoconjunctivitis than asthma. In contrast, early cat contact had more balanced effects in affluent countries, but in non-affluent countries there was a much stronger effect on asthma and eczema than rhinoconjunctivitis.

Among the current exposures for 6-7 year-olds, current paracetamol use was more strongly associated with asthma and rhinoconjunctivitis than

Fig. 1 Mutually adjusted odds ratios and 95% confidence intervals for individual-level associations between risk factors and each of the three diseases, in affluent countries and non-affluent countries. 1A 6-7-year-olds, early exposures. 1B 6-7-year-olds, current exposures. 1C 13-14-year-olds, current exposures. Results from mixed logistic regression models with random intercepts at the school, centre and country levels. Adjusted for sex, mother's level of education and all other variables shown for the same age group. Based on the synthesis sample as shown in Table 3, stratified by country-level affluence. Results for affluent countries shown as diamonds (N = 41,831 aged 6–7; N = 46,932 aged 13–14). Results for non-affluent countries shown as circles (N = 75,032 aged 6–7; N = 177,504 aged 13–14). Results for rhinoconjunctivitis symptoms (R) shown in yellow. Results for asthma symptoms (A) shown in blue. Results for eczema symptoms (E) shown in red. Data points are tabulated in Supplementary Table S2.

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Exposures of interest Age 6-7 years	RC only OR (95% CI)	Asthma only OR (95% CI)	Eczema only OR (95% CI)	RC and Asthma OR (95% CI)	RC and Eczema OR (95% CI)	Asthma and Eczema OR (95% CI)	RC, Asthma and Eczema OR (95% CI)
	Reference group with no disease, $n_0 = 93{,}554$						
	$n_1 = 5508$	$n_1 = 6720$	$n_1 = 5099$	$n_1 = 2503$	$n_1 = 1310$	$n_1 = 1074$	$n_1 = 1095$
Low birthweight	0.98 (0.88, 1.10)	1.16 (1.05, 1.27)	0.85 (0.75, 0.96)	1.14 (0.98, 1.33)	0.96 (0.76, 1.20)	0.90 (0.70, 1.16)	1.14 (0.91, 1.44)
Breastfed ever	0.98 (0.91, 1.05)	0.93 (0.87, 1.00)	1.12 (1.03, 1.21)	0.96 (0.86, 1.06)	1.10 (0.95, 1.28)	0.98 (0.84, 1.15)	1.12 (0.96, 1.32)
Farm animals (prenatal)	1.17 (1.03, 1.34)	1.14 (1.01, 1.28)	1.06 (0.93, 1.22)	1.22 (1.01, 1.47)	1.07 (0.84, 1.37)	1.19 (0.89, 1.58)	1.56 (1.20, 2.03)
Farm animals (1st year)	1.11 (0.99, 1.25)	1.03 (0.92, 1.15)	1.17 (1.03, 1.32)	0.97 (0.82, 1.16)	1.40 (1.13, 1.74)	1.04 (0.80, 1.35)	0.86 (0.66, 1.12)
Cat (1st year)	0.97 (0.88, 1.07)	1.21 (1.12, 1.31)	1.08 (0.99, 1.18)	1.29 (1.14, 1.47)	1.19 (1.00, 1.42)	1.06 (0.89, 1.27)	1.16 (0.97, 1.39)
Dog (1st year)	1.07 (1.00, 1.15)	1.01 (0.94, 1.08)	1.07 (1.00, 1.15)	1.08 (0.98, 1.20)	1.05 (0.92, 1.20)	0.99 (0.86, 1.15)	1.14 (0.99, 1.32)
Paracetamol (1st year)	1.38 (1.29, 1.48)	1.32 (1.24, 1.41)	1.26 (1.17, 1.35)	1.45 (1.30, 1.62)	1.49 (1.29, 1.72)	1.35 (1.14, 1.60)	1.82 (1.52, 2.18)
Antibiotics (1st year)	1.44 (1.36, 1.54)	1.56 (1.47, 1.65)	1.25 (1.17, 1.33)	1.95 (1.77, 2.15)	1.82 (1.60, 2.07)	2.13 (1.84, 2.47)	2.37 (2.03, 2.76)
2 or more siblings	0.98 (0.92, 1.04)	0.96 (0.90, 1.01)	0.94 (0.88, 1.00)	0.98 (0.90, 1.08)	0.91 (0.81, 1.03)	0.88 (0.77, 1.01)	0.99 (0.86, 1.13)
Heavy truck traffic (current)	1.13 (1.06, 1.20)	1.18 (1.12, 1.24)	1.08 (1.01, 1.15)	1.19 (1.09, 1.29)	1.15 (1.02, 1.29)	1.11 (0.98, 1.26)	1.50 (1.32, 1.71)

Exposures of interest Age 6-7 years	RC only OR (95% CI)	Asthma only OR (95% CI)	Eczema only OR (95% CI)	RC and Asthma OR (95% CI)	RC and Eczema OR (95% CI)	Asthma and Eczema OR (95% CI)	RC, Asthma and Eczema OR (95% CI)
	Reference group with no disease, $n_0 = 93{,}554$						
	$n_1 = 5508$	$n_1 = 6720$	$n_1 = 5099$	$n_1 = 2503$	$n_1 = 1310$	$n_1 = 1074$	$n_1 = 1095$
Fast food (current)	0.96 (0.90, 1.02)	1.08 (1.02, 1.15)	0.96 (0.90, 1.03)	1.06 (0.97, 1.16)	1.01 (0.89, 1.14)	1.21 (1.05, 1.38)	0.98 (0.86, 1.13)
Television (current)	0.91 (0.85, 0.98)	1.07 (0.99, 1.15)	0.97 (0.90, 1.05)	1.02 (0.91, 1.14)	0.85 (0.73, 0.99)	1.05 (0.88, 1.25)	0.95 (0.80, 1.12)
Paternal tobacco (current)	1.05 (0.98, 1.12)	1.08 (1.02, 1.15)	1.02 (0.96, 1.10)	1.12 (1.03, 1.23)	0.93 (0.82, 1.06)	1.12 (0.97, 1.29)	1.22 (1.06, 1.40)
Maternal tobacco (current)	1.02 (0.94, 1.11)	1.24 (1.16, 1.33)	1.05 (0.97, 1.14)	1.21 (1.09, 1.36)	1.11 (0.94, 1.30)	1.30 (1.11, 1.53)	1.05 (0.89, 1.24)
Paracetamol (current)	1.90 (1.77, 2.04)	1.96 (1.84, 2.08)	1.34 (1.24, 1.45)	2.86 (2.59, 3.15)	1.91 (1.66, 2.19)	2.17 (1.88, 2.51)	2.92 (2.53, 3.37)
Open fire cooking (current)	0.97 (0.75, 1.25)	1.28 (1.07, 1.55)	1.18 (0.96, 1.45)	1.17 (0.83, 1.67)	1.09 (0.70, 1.72)	1.21 (0.77, 1.91)	0.77 (0.43, 1.39)

Exposures of interest Age 13-14 years	RC only OR (95% CI)	Asthma only OR (95% CI)	Eczema only OR (95% CI)	RC and Asthma OR (95% CI)	RC and Eczema OR (95% CI)	Asthma and Eczema OR (95% CI)	RC, Asthma and Eczema OR (95% CI)
	Reference group with no disease, $n_0 = 170,542$						
	$n_1 = 19,858$	$n_1 = 13,585$	$n_1 = 7104$	$n_1 = 6557$	$n_1 = 3219$	$n_1 = 1554$	$n_1 = 2017$
2 or more siblings	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	1.06 (1.00, 1.12)	1.05 (0.99, 1.11)	1.18 (1.09, 1.29)	1.06 (0.95, 1.19)	1.12 (1.01, 1.24)
Heavy truck traffic (current)	1.19 (1.16, 1.23)	1.14 (1.09, 1.18)	1.26 (1.20, 1.33)	1.30 (1.23, 1.37)	1.44 (1.34, 1.55)	1.47 (1.33, 1.64)	1.56 (1.42, 1.71)
Fast food (current)	1.04 (1.01, 1.08)	1.06 (1.02, 1.10)	1.06 (1.00, 1.12)	1.13 (1.07, 1.19)	1.12 (1.04, 1.21)	1.13 (1.01, 1.26)	1.13 (1.02, 1.24)
Television (current)	1.03 (0.98, 1.08)	1.08 (1.02, 1.15)	1.09 (1.01, 1.19)	0.97 (0.89, 1.06)	1.23 (1.08, 1.41)	1.21 (1.01, 1.46)	0.80 (0.69, 0.92)
Paternal tobacco (current)	1.08 (1.04, 1.11)	1.10 (1.05, 1.14)	1.13 (1.07, 1.19)	1.14 (1.07, 1.20)	1.22 (1.13, 1.32)	1.16 (1.04, 1.30)	1.26 (1.14, 1.39)
Maternal tobacco (current)	1.09 (1.05, 1.14)	1.20 (1.15, 1.26)	1.07 (0.99, 1.14)	1.27 (1.19, 1.35)	1.19 (1.08, 1.31)	1.22 (1.06, 1.39)	1.32 (1.18, 1.49)
Paracetamol (current)	1.62 (1.56, 1.68)	1.69 (1.62, 1.76)	1.36 (1.29, 1.44)	2.34 (2.21, 2.47)	2.16 (2.00, 2.34)	2.12 (1.89, 2.36)	2.98 (2.71, 3.29)
Open fire cooking (current)	1.15 (1.05, 1.27)	1.12 (1.01, 1.25)	1.33 (1.15, 1.53)	1.09 (0.92, 1.28)	1.50 (1.22, 1.84)	1.93 (1.49, 2.50)	2.22 (1.76, 2.81)

Table 4. (Continued) Multi outcome models of fully adjusted[a] within school effects of exposures compared to a reference group with no disease. Mixed logistic regression models with random intercepts at the school, centre and country levels. *a. Adjusted for sex, mother's level of education and all other variables in the table for that age group*

Age group	Exposures of Interest	Asthma v Eczema OR (95% CI)	Asthma v Rhinoconjunctivitis OR (95% CI)	Rhinoconjunctivitis v Eczema OR (95% CI)
6–7 years		n = 11,819	n = 12,228	n = 10,607
	Low birthweight	1.40 (1.19, 1.64)	1.16 (0.99, 1.35)	1.11 (0.94, 1.32)
	Breastfed ever	0.85 (0.76, 0.94)	0.94 (0.85, 1.05)	0.89 (0.80, 1.00)
	Farm animals (prenatal)	1.03 (0.85, 1.23)	0.99 (0.82, 1.18)	1.04 (0.86, 1.26)
	Farm animals (1st year)	0.90 (0.76, 1.06)	0.89 (0.75, 1.05)	0.98 (0.83, 1.17)
	Cat (1st year)	1.12 (0.99, 1.26)	1.27 (1.11, 1.44)	0.83 (0.73, 0.96)
	Dog (1st year)	0.94 (0.85, 1.04)	0.97 (0.87, 1.07)	0.95 (0.86, 1.05)
	Paracetamol (1st year)	1.05 (0.95, 1.16)	0.96 (0.86, 1.06)	1.07 (0.96, 1.19)
	Antibiotics (1st year)	1.26 (1.16, 1.38)	1.12 (1.03, 1.23)	1.14 (1.03, 1.25)
	2 or more siblings	1.01 (0.93, 1.10)	0.99 (0.90, 1.08)	1.03 (0.94, 1.13)
	Heavy truck traffic (current)	1.08 (1.00, 1.17)	1.05 (0.97, 1.14)	1.06 (0.97, 1.16)
	Fast food (current)	1.12 (1.02, 1.22)	1.12 (1.03, 1.23)	1.00 (0.91, 1.10)
	Television (current)	1.13 (1.01, 1.26)	1.16 (1.04, 1.29)	0.92 (0.82, 1.03)
	Paternal tobacco (current)	1.03 (0.94, 1.12)	1.03 (0.94, 1.13)	1.02 (0.92, 1.12)
	Maternal tobacco (current)	1.16 (1.04, 1.29)	1.21 (1.08, 1.35)	0.94 (0.84, 1.07)
	Paracetamol (current)	1.45 (1.31, 1.60)	1.03 (0.93, 1.14)	1.48 (1.32, 1.65)
	Open fire cooking (current)	1.02 (0.77, 1.35)	1.32 (0.95, 1.83)	0.72 (0.51, 1.01)
13–14 years		n = 20,689	n = 33,443	n = 26,962
	2 or more siblings	0.94 (0.87, 1.01)	0.99 (0.94, 1.05)	0.96 (0.90, 1.03)
	Heavy truck traffic (current)	0.92 (0.86, 0.99)	0.97 (0.92, 1.02)	0.93 (0.87, 0.98)

(continued)

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Age group	Exposures of Interest	Asthma v Eczema OR (95% CI)	Asthma v Rhinoconjunctivitis OR (95% CI)	Rhinoconjunctivitis v Eczema OR (95% CI)
	Fast food (current)	1.01 (0.94, 1.08)	0.99 (0.94, 1.04)	1.00 (0.94, 1.06)
	Television (current)	0.98 (0.88, 1.09)	1.06 (0.98, 1.15)	0.96 (0.87, 1.06)
	Paternal tobacco (current)	0.96 (0.89, 1.03)	1.01 (0.96, 1.06)	0.96 (0.90, 1.03)
	Maternal tobacco (current)	1.15 (1.06, 1.26)	1.13 (1.06, 1.21)	1.02 (0.94, 1.11)
	Paracetamol (current)	1.17 (1.09, 1.26)	1.02 (0.97, 1.08)	1.16 (1.09, 1.24)
	Open fire cooking (current)	0.89 (0.74, 1.06)	1.05 (0.91, 1.21)	0.80 (0.68, 0.95)

Table 5. (Continued) Fully adjusted[a] unimorbid two-way models. Mixed logistic regression models with random intercepts at the school, centre and country levels. *a. Adjusted for sex, mother's level of education and all other variables in the table for that age group*

with eczema. Open fire cooking was more strongly associated with both asthma and eczema than rhinoconjunctivitis but the confidence intervals were wide. Maternal smoking was more strongly associated with asthma than with eczema or rhinoconjunctivitis. Affluent centres showed a stronger effect of open fire cooking on asthma and rhinoconjunctivitis, whereas in non-affluent centres the stronger effect was on asthma and eczema.

Among 13-14 year-olds, similar to the younger children, maternal smoking had a stronger association with asthma than with either eczema or rhinoconjunctivitis, and current paracetamol showed a stronger association with asthma and rhinoconjunctivitis than with eczema. The biggest difference between affluent and non-affluent countries was observed for open fire cooking. In affluent countries, there were stronger associations with eczema than with asthma or rhinoconjunctivitis, although it is important to note that the confidence intervals were exceptionally large due to the rarity of cooking on open fires in the affluent centres.

DISCUSSION

Overview of findings

This is the largest and broadest overview to date of lifestyle and environmental risk factors for symptoms of non-infective rhinoconjunctivitis among children. It is the first comprehensive analysis of this condition, which models multiple risk factors together to compare their mutually adjusted individual-level and population (school)-level associations in a multilevel framework. Due to the multiple comparisons made, and the large size of our sample, we concentrate our interpretation upon the overall patterns of results and on specific findings with more extreme levels of statistical significance.

Generally, associations with exposures averaged at the school level were similar in direction and magnitude to those ascertained at the child level, as we found also for symptoms of asthma and eczema. As we have argued elsewhere,[20,21] this helps to exclude reverse causation, particularly for exposures such as early paracetamol and antibiotic use which may be related to prodromal disease, or pets which may

be avoided by allergic families. An exception are the results for breastfeeding, showing a borderline significant inverse association with asthma symptoms, a significantly positive association with eczema symptoms, and a null association with rhinoconjunctivitis at the individual level (Table 3). Nevertheless, the association of breastfeeding with rhinoconjunctivitis at the school level is strongly and significantly inverse (Table 2), perhaps indicating confounding by socioeconomic or other unmeasured characteristics of the school catchment population. This contrasts with the pattern of school-level associations of breastfeeding with symptoms of asthma[20] and eczema,[21] which were weakly positive but non-significant.

Many of the risk factor associations observed for symptoms of rhinoconjunctivitis were similar to those previously reported for symptoms of asthma or eczema in ISAAC Phase Three.[6-21] Since the 3 diseases cluster together at the individual level, it is possible that associations observed for one disease could be influenced by risk factors for other conditions in the triad. An innovative use of ISAAC data in this paper is the analysis of rhinoconjunctivitis, asthma and eczema, singly and in combination.

As expected, we found that associations with multimorbidity (combinations of 2 or 3 diseases) were stronger than for each disease alone (unimorbidity). However, the relationships of risk factors with each disease in the absence of the others were of similar direction and magnitude to the results for each condition modelled separately. Thus, multimorbidity is not the sole explanation of the common epidemiological patterns across these three diseases.

For many risk factors, associations were consistent across the 3 diseases, between the 2 age groups, and between countries with different levels of per capita Gross National Income. This similarity of epidemiology strongly suggests that there are common biological mechanisms for these 3 diseases, which operate in both affluent and less affluent settings. The most striking example of this in our ISAAC dataset is current paracetamol exposure, which was consistently associated with each of the 3 diseases, within schools and between schools, in both age groups and in richer and poorer countries, although somewhat more strongly with rhinoconjunctivitis and asthma than with eczema.

Shared mechanisms do not exclude the possibility of disease-specific pathways, which may differ between higher and lower income countries. An example of the latter is the inverse association of seasonal rhinoconjunctivitis with number of siblings and childhood exposure to the farm environment. This is well established from large epidemiological studies in Europe and confirmed by objective markers of allergic sensitisation.[26] This pattern is consistent with our findings for rhinoconjunctivitis symptoms in affluent countries but contrasts with the increased risk of these symptoms among children from larger families and those exposed to farm animals in poorer countries.

Strengths and limitations

ISAAC Phase Three has substantial advantages in terms of large sample sizes drawn from diverse study centres worldwide, who adopted standardised methods of data collection. Reliance solely upon questionnaires completed by parents (for the 6-7-year-olds) or participants (for the 13-14-year-olds) is a limitation, both for definition of disease outcomes and for ascertainment of risk factors. On the other hand, the questionnaire methodology maintained high response rates in each centre.

Misclassification of disease or risk factor information could be non-systematic, leading to weaker associations, or systematic, potentially exaggerating, or masking associations. A particular concern would be individual differences in the threshold for reporting of symptoms, which could exaggerate clustering of the 3 complaints within individual children. This is unlikely to affect risk factor associations in our unimorbid analysis, where similarity in the epidemiological patterns for the each of the 3 diseases (in the absence of the others, Table 4) would be biased only if reporting of all 3 diseases were altered by the presence of the risk factor (or conversely, reporting of the common risk factor were biased to a similar degree by the presence of each of the 3 diseases).

A particular limitation of ISAAC Phase Three is the lack of objective information on allergic

sensitisation. This was measured by skin prick testing and serum allergen-specific IgE in a separate study of more than 50,000 10-11-year-old children in 30 centres from 22 countries (ISAAC Phase Two).[3-5,27] Although (as expected) symptoms of rhinoconjunctivitis, asthma and eczema were more common among children with positive skin prick tests, these associations were substantially weaker in less affluent settings. The proportion of each disease attributable to skin prick positivity in centres from lower-income countries (per capita GNI < USD 9200 in 2001) was 14% for rhinoconjunctivitis, 20% for asthma but only 1% for eczema. The corresponding population attributable fractions (PAFs) in higher-income countries were 61% for rhinoconjunctivitis, 46% for asthma, and 28% for eczema. The PAF estimates were very similar when serum allergen-specific IgE was used as the measure of allergic sensitisation.[4]

Throughout, ISAAC has focused upon the combination of nasal and conjunctival symptoms (in the absence of intercurrent infection) as the most relevant definition of rhinoconjunctivitis because non-infective rhinitis alone (without itchy eyes) is less strongly associated with skin prick positivity (PAFs of 5% in less affluent centres and 10% in more affluent centres).[27] More recent studies, among adolescents[28] and adults[29] have confirmed a stronger association of allergic sensitisation with rhinoconjunctivitis than with rhinitis alone.

A shared non-allergic mechanism for "atopic diseases"?

In recent decades, two models of multimorbidity have been proposed to explain the occurrence of 2 or more "atopic diseases" (asthma, rhinitis, and eczema, sometimes extended also to food allergy). The term "united airway disease" has been proposed for the coexistence of asthma and rhinitis in the same patient at the same time.[30-32] The concept of the "atopic march" applies to the sequential development of eczema, asthma, and rhinitis (usually in that order) through childhood and adolescence.[33,34] Discussion of both concepts has tended to focus upon IgE-mediated allergic mechanisms and Th2-immune inflammatory pathways as an explanation for concurrent and longitudinal clustering of the 3 diseases.

However, it is recognised that several distinct pathways and mechanisms are likely to be involved in the atopic march, some of them common and some disease-specific.[34] Non-allergic airway inflammation, defects of mucosal defence, and exogenous cofactors (including microbes, pollutants and smoking) have been proposed as "treatable traits" underlying united airway disease,[32] in addition to the close association of both asthma and rhinitis with IgE sensitisation, particularly to multiple allergens.[35]

Genome-wide association studies have shown a mixture of common and disease-specific signals for asthma, hay fever, and eczema[36] illustrated by triangle plots derived from unimorbid case-only comparisons similar to those we have shown in Table 5 and Figs. S3–S8. Filaggrin (*FLG*) variants are specifically associated with eczema, whereas other genome-wide significant loci such as *IL6R* show almost perfect symmetry in association with each of the 3 diseases. A bioinformatics (data-mining) analysis of protein interactions found that asthma, rhinitis, and eczema shared more associated proteins than would be expected by chance and identified 15 pathways potentially involved in the multimorbidity of asthma, rhinitis, and eczema, although many of these are related to Th2-immune signalling pathways.[37]

Epidemiological evidence for non-allergic mechanisms underlying coexistence of asthma, rhinitis, and eczema emerges from the collaborative analysis of European birth cohorts by the MeDALL consortium.[38] Among over 8000 children followed from birth to 4 and 8 years of age, IgE sensitisation to common food and aero-allergens at age 4 years accounted for only 38% of the co-occurrence of 2 or more conditions (asthma, rhinitis, and eczema) at age 8 years. In relative terms, the strength of the association among the 3 diseases was higher in non-sensitised children, although the excess comorbidity was greater among those who were sensitised, due to a higher baseline risk of disease. Among the sensitised children, about a quarter of the observed comorbidity was not due to chance, whereas among non-sensitised children the non-chance proportion was more than half at age 8 years. Comorbidity at age 4 years was strongly predictive of comorbidity at age 8 years. All these observations led the MeDALL investigators to propose "a new vision of

multimorbidity independent of IgE sensitisation",[39] which would be entirely consistent with our observations of common epidemiological patterns for symptoms of rhinoconjunctivitis, asthma, and eczema in 2 age groups of children in both affluent and non-affluent countries worldwide.

CONCLUSIONS

Most of the environmental and lifestyle correlates of rhinoconjunctivitis, asthma, and eczema in childhood display similarity across the 3 conditions, even in less affluent settings where allergic sensitisation (as conventionally defined) is less likely to explain the concordant epidemiological patterns. This supports the view that mechanisms other than IgE-mediated tissue inflammation may contribute a substantial proportion of the clustering of these "atopic diseases" within individuals (concurrently and sequentially) and at the population level.

Author contributions

Data collection was co-ordinated by I.A., P.E., N.P., L.G-M. and D.S. and implemented by the ISAAC Phase Three Study Group. This data analysis and presentation were conceived by C.R., R.S., N.P. and D.S. Statistical modelling was performed by C.R. as part of PhD studies supervised by R.S., N.P. and D.S. The manuscript was drafted by C.R. and D.S. and critically reviewed by all named authors.

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The funders had no involvement in the conduct of the research (collection, analysis or preparation of data), nor in the writing of this report, nor in the decision to submit the article for publication.

Consent for publication

No additional consent (from institutions or funders) is required for publication.

Ethical approval

Not applicable, as this is secondary analysis of an existing, publicly available dataset.

Availability of data

The ISAAC Phase Three datasets, on which this article is based, and associated survey documentation, have been deposited at the UK Data Archive for use by *bona fide* researchers on application via the following URL: http://discover.ukdataservice.ac.uk/catalogue?sn=8131 (https://doi.org/10.5255/UKDA-SN-8131-1)

Declaration of competing interest

The authors report no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100123.

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REFERENCES

1. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, ISAAC Steering Committee. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tubercul Lung Dis*. 2005;9:10–16.
2. Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483–491.
3. Weiland SK, Björkstén B, Brunekreef B, et al. Phase II of the international study of asthma and allergies in childhood (ISAAC II): rationale and methods. *Eur Respir J*. 2004;24:406–412.
4. Weinmayr G, Weiland SK, Björkstén B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med*. 2007;176:565–574.
5. Flohr C, Weiland SK, Weinmayr G, et al. The role of atopic sensitization in flexural eczema: findings from the international study of asthma and allergies in childhood phase two. *J Allergy Clin Immunol*. 2008;121:141–147.
6. Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and later childhood and risk of asthma, rhinoconjunctivitis and eczema in 6 to 7 year old children: ISAAC Phase Three. *Lancet*. 2008;362:1039–1048.
7. Foliaki S, Pearce N, Björkstén B, et al. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: international Study of Asthma and Allergies in Childhood Phase III. *J Allergy Clin Immunol*. 2009;124:982–989.
8. Björkstén B, Ait-Khaled N, Asher MI, Clayton TO, Robertson C, ISAAC Phase Three Study Group. Global analysis of breast feeding and risk of symptoms of asthma, rhinoconjunctivitis and eczema in 6-7 year old children: ISAAC Phase Three. *Allergol Immunopathol*. 2011;39:318–325.
9. Brunekreef B, von Mutius E, Wong G, et al. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis and eczema. *Epidemiology*. 2012;23:742–750.
10. Brunekreef B, von Mutius E, Wong GK, Odhiambo JA, Clayton TO, ISAAC Phase Three Study Group. Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study. *Int J Epidemiol*. 2012;41:753–761.
11. Brunekreef B, Stewart AW, Anderson HR, et al. Self-reported truck traffic on the street of residence and symptoms of asthma and allergic Disease: a global relationship in ISAAC Phase 3. *Environ Health Perspect*. 2009;117:1791–1798.
12. Ellwood P, Asher MI, García-Marcos L, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the international study of asthma and allergies in childhood (ISAAC) phase three. *Thorax*. 2013;68:351–360.
13. Mitchell EA, Beasley R, Björkstén B, et al. The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three. *Clin Exp Allergy*. 2013;43:73–84.
14. Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J, ISAAC Phase Three Study Group. The association between tobacco and the risk of asthma, rhinoconjunctivitis and eczema in children and adolescents: analyses from Phase Three of the ISAAC programme. *Thorax*. 2012;67:941. U128.
15. Wong GWK, Brunekreef B, Ellwood P, et al. Cooking fuels and prevalence of asthma: a global analysis of phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet Respir Med*. 2013;1:386–394.
16. Mitchell EA, Clayton T, García-Marcos L, et al. Birthweight and the risk of atopic diseases: the ISAAC Phase III study. *Pediatr Allergy Immunol*. 2014;25:264–270.
17. Strachan DP, Ait-Khaled N, Foliaki S, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the international study of asthma and allergies in childhood. *Clin Exp Allergy*. 2015;45:126–136.
18. Beasley RW, Clayton TO, Crane J, et al. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: international study of asthma and allergies in childhood phase three. *Am J Respir Crit Care Med*. 2011;183:171–178.
19. Garcia-Marcos L, Robertson CF, Anderson HR, et al. Does migration affect asthma, rhinoconjunctivitis and eczema prevalence? Global findings from the international study of asthma and allergies in childhood. *Int J Epidemiol*. 2014;43:1846–1854.
20. Silverwood RJ, Rutter CE, Mitchell EA, et al. Are environmental risk factors for current wheeze in the International Study of Asthma and Allergies in Childhood (ISAAC) phase three due to reverse causation? *Clin Exp Allergy*. 2019;49:430–441.
21. Rutter CE, Silverwood RJ, Williams HC, et al. Are environmental factors for atopic eczema in ISAAC Phase Three due to reverse causation? *J Invest Dermatol*. 2019;139:1023–1036.
22. The World Bank. *GNI Per Capita, Atlas Method (Current US$)*; 2016. http://data.worldbank.org/indicator/NY.GNP.PCAP.CD. Accessed October 24, 2016.
23. Central Intelligence Agency. *The World Factbook*; 2002. www.cia.gov/library/publications/download/download-2002/.
24. The World Bank. *World Bank GNI Per Capita Operational Guidelines and Analytical Classifications*; 2016. http://siteresources.worldbank.org/DATASTATISTICS/Resources/OGHIST.xls. Accessed February 1, 2017.
25. *StataCorp. Stata Statistical Software: Release* version 15. College Station, TX: StataCorp LLC; 2017.
26. Genuneit J, Strachan DP, Büchele G, et al. The combined effects of family size and farm exposure on childhood hay fever and atopy. *Pediatr Allergy Immunol*. 2013;24:293–298.
27. Weinmayr G, Forastiere F, Weiland SK, et al. International variation in prevalence of rhinitis and its relation with sensitization to perennial and seasonal allergens. *Eur Respir J*. 2008;32:1250–1261.
28. Cibella F, Ferrante G, Cuttitta G, et al. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res*. 2015;7:44–50.
29. Siroux V, Boudier A, Nadif R, Lupinek C, Valenta R, Bousquet J. Association between asthma, rhinitis, and conjunctivitis multimorbidities with molecular IgE sensitization in adults. *Allergy*. 2018;74:824–826.

30. Licari A, Castagnoli R, Denicolo CF, Rossini L, Marseglia A, Marseglia GL. The nose and the lung: united airway disease? *Front Pediatr*. 2017;5:44.

31. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. *J Asthma Allergy*. 2016;9:93–100.

32. Yii ACA, Tay TR, Choo XN, Koh MSY, Tee AKH, Wang DY. Precision medicine in united airway disease. A "treatable traits" approach. *Allergy*. 2018;73:1964–1978.

33. Davidson WF, Leung DYM, Beck LA, et al. Report from the national Institute of allergy and infectious diseases workshop on "atopic dermatitis and the atopic march: mechanisms and interventions". *J Allergy Clin Immunol*. 2019;143:894–913.

34. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. *J Allergy Clin Immunol*. 2019;143:46–55.

35. Siroux V, Ballardini N, Soler M, et al. The asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults. *Allergy*. 2018;73:1447–1458.

36. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. 2017;49:1752–1757.

37. Aguilar D, Pinart M, Koppelmann G, et al. Computational analysis of multimorbidity between asthma, eczema and rhinitis. *PloS One*. 2017;12, e0179125.

38. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respr Med*. 2014;2:131–140.

39. Anto JM, Bousquet J, Akdis M, et al. Mechanisms of the development of Allergy (MeDALL): introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol*. 2017;139:388–399.

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SUPPORTING MATERIAL

Table S1: Risk factor definitions.

Table S2: Single outcome models of fully adjusted within school effects of exposures using the synthesis sample, stratified by country-level affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Table S3: Fully adjusted unimorbid two-way models split by country affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Figure S1. Synthesis sample data flowchart, age 6-7 years.

Figure S2. Synthesis sample data flowchart, age 13-14 years.

Figure S3. Triangular graphs showing unimorbid two-way comparisons of early life risk factor effects for 6-7-year-old children.

Figure S4. Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 6-7-year-old children.

Figure S5. Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 13-14-year-old adolescents.

Figure S6. Triangular graphs showing unimorbid two-way comparisons of effects of early life risk factors for 6-7-year-old children in affluent and non-affluent countries.

Figure S7. Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 6-7-year-old children in affluent and non-affluent countries.

Figure S8. Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 13-14-year-old adolescents in affluent and non-affluent countries.

Table S1: Risk factor definitions

Risk Factors for ages 6-7	Question (asked to parent)	Positive Response
Low birthweight	What was the weight of your child when he / she was born?	Less than 2.5kg
Breastfed ever	Was your child breastfed?	Yes
Farm animals (prenatal)	Has the child's mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child?	Yes
Farm animals (1st year)	In your child's first year of life, did he / she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)?	Yes
Cat (1st year)	Did you have a cat in your home during the first year of your child's life?	Yes
Dog (1st year)	Did you have a dog in your home during the first year of your child's life?	Yes
Paracetamol (1st year)	In the first 12 months of your child's life, did you usually give paracetamol for fever?	Yes
Antibiotics (1st year)	In the first 12 months of your child's life, did your child have any antibiotics?	Yes
2 or more siblings	How many older and younger brothers and sisters does your child have?	Total of 2 or more
Heavy truck traffic (current)	How often do trucks pass through the street where you live, on weekdays?	Frequently or almost the whole day
Fast food (current)	In the past 12 months, how often, on average did your child eat fast food / burgers?	At least once a week
Television (current)	During a normal week, how many hours a day (24 hours) does your child watch television?	At least one hour per day
Paternal tobacco (current)	Does your child's father (or male guardian) smoke cigarettes?	Yes
Maternal tobacco (current)	Does your child's mother (or female guardian) smoke cigarettes?	Yes
Paracetamol (current)	In the past 12 months, how often, on average, have you given your child paracetamol?	At least once per month
Open fire cooking (current)	In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other	Any that include open fires

Risk Factors for ages 13-14	Question (asked to child)	Positive Response
2 or more siblings	How many older and younger brothers and sisters do you have?	Total of 2 or more
Heavy truck traffic (current)	How often do trucks pass through the street where you live, on weekdays?	Frequently or almost the whole day
Fast food (current)	In the past 12 months, how often, on average did you eat fast food / burgers?	At least once a week
Television (current)	During a normal week, how many hours a day (24 hours) do you watch television?	At least one hour per day
Paternal tobacco (current)	Does your father (or male guardian) smoke cigarettes?	Yes
Maternal tobacco (current)	Does your mother (or female guardian) smoke cigarettes?	Yes
Paracetamol (current)	In the past 12 months, how often, on average, have you taken paracetamol?	At least once per month
Open fire cooking (current)	In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other	Any that include open fires

Table S2: Single outcome models of fully adjusted[A] within school effects of exposures using the synthesis sample[B], stratified by country-level affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Age	Exposure	Affluent Countries (n = 41,831)			Non-affluent Countries (n = 75,032)		
		Rhinoconjunctivitis OR (95% CI)	Asthma OR (95% CI)	Eczema OR (95% CI)	Rhinoconjunctivitis OR (95% CI)	Asthma OR (95% CI)	Eczema OR (95% CI)
6-7 years	Low birthweight	1.02 (0.89, 1.16)	1.17 (1.03, 1.31)	0.93 (0.80, 1.07)	1.05 (0.95, 1.16)	1.14 (1.03, 1.26)	0.87 (0.77, 0.99)
	Breastfed ever	1.03 (0.96, 1.11)	1.02 (0.96, 1.10)	1.15 (1.06, 1.25)	0.96 (0.89, 1.04)	0.87 (0.81, 0.94)	1.05 (0.96, 1.15)
	Farm animals (prenatal)	1.16 (0.98, 1.38)	0.98 (0.83, 1.14)	1.00 (0.83, 1.21)	1.20 (1.07, 1.34)	1.32 (1.18, 1.49)	1.20 (1.06, 1.36)
	Farm animals (1st year)	0.88 (0.75, 1.03)	0.94 (0.81, 1.08)	0.95 (0.80, 1.13)	1.19 (1.07, 1.33)	1.02 (0.91, 1.13)	1.25 (1.11, 1.40)
	Cat (1st year)	1.05 (0.95, 1.16)	1.10 (1.01, 1.20)	0.99 (0.90, 1.09)	1.11 (1.01, 1.22)	1.36 (1.24, 1.49)	1.23 (1.11, 1.36)
	Dog (1st year)	1.05 (0.97, 1.14)	0.98 (0.91, 1.06)	0.98 (0.90, 1.07)	1.07 (1.00, 1.15)	1.06 (0.99, 1.14)	1.10 (1.02, 1.18)
	Paracetamol (1st year)	1.39 (1.27, 1.52)	1.41 (1.30, 1.53)	1.28 (1.17, 1.41)	1.40 (1.31, 1.50)	1.30 (1.21, 1.39)	1.31 (1.22, 1.41)
	Antibiotics (1st year)	1.60 (1.49, 1.72)	1.70 (1.59, 1.82)	1.43 (1.33, 1.54)	1.56 (1.46, 1.66)	1.62 (1.52, 1.73)	1.36 (1.27, 1.45)
	2 or more siblings	0.87 (0.81, 0.94)	0.91 (0.85, 0.98)	0.95 (0.88, 1.02)	1.06 (1.00, 1.13)	1.01 (0.95, 1.07)	0.93 (0.87, 1.00)
	Heavy truck traffic (current)	1.16 (1.08, 1.24)	1.16 (1.09, 1.24)	1.08 (1.01, 1.17)	1.17 (1.11, 1.24)	1.20 (1.14, 1.27)	1.14 (1.07, 1.21)
	Fast food (current)	0.99 (0.92, 1.06)	1.07 (1.00, 1.14)	1.05 (0.97, 1.13)	0.98 (0.92, 1.05)	1.09 (1.03, 1.16)	0.96 (0.89, 1.03)
	Television (current)	0.88 (0.81, 0.95)	1.05 (0.98, 1.14)	0.92 (0.85, 1.00)	1.00 (0.92, 1.08)	1.05 (0.97, 1.14)	1.01 (0.93, 1.11)
	Paternal tobacco (current)	1.04 (0.97, 1.11)	1.11 (1.03, 1.18)	1.06 (0.98, 1.14)	1.10 (1.03, 1.17)	1.10 (1.03, 1.17)	1.03 (0.96, 1.11)
	Maternal tobacco (current)	1.06 (0.98, 1.15)	1.20 (1.12, 1.29)	1.01 (0.92, 1.10)	1.03 (0.94, 1.13)	1.22 (1.11, 1.33)	1.12 (1.02, 1.24)
	Paracetamol (current)	2.19 (2.01, 2.40)	2.36 (2.19, 2.56)	1.65 (1.50, 1.81)	1.94 (1.82, 2.07)	1.90 (1.78, 2.02)	1.35 (1.25, 1.46)
	Open fire cooking (current)	1.52 (1.05, 2.21)	1.62 (1.17, 2.24)	1.09 (0.72, 1.65)	0.88 (0.71, 1.09)	1.10 (0.92, 1.32)	1.13 (0.94, 1.36)

Age	Exposure	Affluent Countries (n = 46,932)			Non-Affluent Countries (n = 177,504)		
		Rhinoconjunctivitis OR (95% CI)	Asthma OR (95% CI)	Eczema OR (95% CI)	Rhinoconjunctivitis OR (95% CI)	Asthma OR (95% CI)	Eczema OR (95% CI)
13-14 years	2 or more siblings	1.00 (0.94, 1.05)	1.01 (0.95, 1.07)	1.06 (0.97, 1.16)	1.05 (1.02, 1.09)	1.03 (0.99, 1.07)	1.08 (1.03, 1.14)
	Heavy truck traffic (current)	1.22 (1.15, 1.28)	1.15 (1.08, 1.22)	1.33 (1.22, 1.45)	1.23 (1.20, 1.27)	1.21 (1.17, 1.26)	1.31 (1.25, 1.36)
	Fast food (current)	1.06 (1.00, 1.11)	1.03 (0.97, 1.09)	1.06 (0.97, 1.16)	1.06 (1.02, 1.09)	1.08 (1.04, 1.12)	1.06 (1.02, 1.11)
	Television (current)	0.98 (0.90, 1.08)	1.05 (0.95, 1.16)	0.95 (0.83, 1.10)	1.01 (0.97, 1.06)	1.01 (0.95, 1.06)	1.10 (1.03, 1.18)
	Paternal tobacco (current)	1.02 (0.97, 1.08)	1.10 (1.03, 1.16)	1.04 (0.95, 1.14)	1.12 (1.09, 1.16)	1.11 (1.07, 1.16)	1.18 (1.13, 1.23)
	Maternal tobacco (current)	1.13 (1.06, 1.20)	1.27 (1.20, 1.36)	1.07 (0.97, 1.19)	1.14 (1.09, 1.19)	1.19 (1.14, 1.25)	1.12 (1.06, 1.19)
	Paracetamol (current)	1.96 (1.85, 2.08)	1.99 (1.87, 2.11)	1.76 (1.61, 1.93)	1.70 (1.65, 1.76)	1.75 (1.68, 1.81)	1.54 (1.48, 1.61)
	Open fire cooking (current)	0.82 (0.62, 1.07)	1.06 (0.82, 1.37)	1.63 (1.16, 2.29)	1.20 (1.11, 1.30)	1.21 (1.11, 1.33)	1.46 (1.32, 1.63)

[A]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

[B]Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest.

Table S3: Fully adjusted[A] unimorbid two-way models split by country affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Exposure of Interest	Asthma v Eczema, fully adjusted models[A]		Rhinoconjunctivitis v Asthma, fully adjusted models[A]		Eczema v Rhinoconjunctivitis, fully adjusted models[A]	
Age 6-7 years	Affluent countries n=5,172	Non-affluent countries n=6,647	Affluent countries n=5,189	Non-affluent countries n=7,039	Affluent countries n=4,347	Non-affluent countries n=6,260
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Low birthweight	1.42 (1.10, 1.82)	1.40 (1.13, 1.72)	0.81 (0.63, 1.05)	0.90 (0.74, 1.09)	0.85 (0.63, 1.14)	0.93 (0.75, 1.15)
Breastfed ever	0.86 (0.75, 0.99)	0.84 (0.72, 0.99)	1.03 (0.89, 1.18)	1.09 (0.94, 1.27)	1.12 (0.96, 1.31)	1.10 (0.93, 1.29)
Farm animals (prenatal)	0.85 (0.63, 1.16)	1.13 (0.90, 1.42)	1.23 (0.90, 1.68)	0.92 (0.74, 1.15)	0.85 (0.60, 1.20)	1.01 (0.80, 1.27)
Farm animals (1st year)	1.08 (0.82, 1.43)	0.82 (0.67, 1.02)	1.00 (0.76, 1.33)	1.21 (0.98, 1.48)	1.02 (0.75, 1.40)	0.99 (0.81, 1.23)
Cat (1st year)	1.08 (0.92, 1.27)	1.17 (0.98, 1.39)	0.91 (0.75, 1.09)	0.69 (0.57, 0.82)	1.06 (0.87, 1.29)	1.35 (1.12, 1.63)
Dog (1st year)	1.02 (0.87, 1.18)	0.89 (0.78, 1.01)	1.09 (0.93, 1.29)	1.00 (0.88, 1.14)	0.93 (0.78, 1.11)	1.12 (0.98, 1.27)
Paracetamol (1st year)	1.15 (0.99, 1.35)	0.98 (0.86, 1.11)	1.04 (0.88, 1.23)	1.05 (0.92, 1.20)	0.88 (0.73, 1.05)	0.97 (0.86, 1.11)
Antibiotics (1st year)	1.26 (1.11, 1.43)	1.27 (1.12, 1.43)	0.87 (0.76, 1.00)	0.90 (0.80, 1.02)	0.93 (0.81, 1.08)	0.84 (0.75, 0.95)
2 or more siblings	0.98 (0.86, 1.12)	1.04 (0.93, 1.18)	0.89 (0.77, 1.03)	1.11 (0.99, 1.24)	1.11 (0.96, 1.30)	0.89 (0.79, 1.00)
Heavy truck traffic (current)	1.03 (0.91, 1.17)	1.11 (1.00, 1.24)	0.91 (0.80, 1.05)	0.98 (0.88, 1.09)	1.04 (0.90, 1.20)	0.89 (0.80, 1.00)
Fast food (current)	0.99 (0.87, 1.13)	1.20 (1.07, 1.36)	0.93 (0.81, 1.07)	0.87 (0.77, 0.97)	1.07 (0.92, 1.25)	0.96 (0.85, 1.09)
Television (current)	1.19 (1.02, 1.38)	1.06 (0.90, 1.24)	0.83 (0.71, 0.97)	0.88 (0.76, 1.02)	1.09 (0.92, 1.28)	1.13 (0.96, 1.33)
Paternal tobacco (current)	1.02 (0.89, 1.17)	1.01 (0.90, 1.15)	0.93 (0.81, 1.07)	1.00 (0.89, 1.13)	1.04 (0.89, 1.21)	0.96 (0.85, 1.09)
Maternal tobacco (current)	1.28 (1.11, 1.48)	1.00 (0.84, 1.19)	0.81 (0.70, 0.95)	0.84 (0.71, 1.00)	0.93 (0.78, 1.10)	1.22 (1.03, 1.45)
Paracetamol (current)	1.58 (1.34, 1.87)	1.39 (1.22, 1.58)	0.94 (0.79, 1.12)	1.00 (0.89, 1.13)	0.67 (0.55, 0.82)	0.67 (0.59, 0.77)
Open fire cooking (current)	1.21 (0.62, 2.35)	1.00 (0.73, 1.38)	1.00 (0.50, 2.03)	0.72 (0.49, 1.04)	0.82 (0.37, 1.81)	1.54 (1.04, 2.26)
Age 13-14 years	Affluent countries n=4,774	Non-affluent countries n=15,915	Affluent countries n=7,941	Non-affluent countries n=25,502	Affluent countries n=5,557	Non-affluent countries n=21,405
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2 or more siblings	0.93 (0.80, 1.07)	0.95 (0.87, 1.03)	0.98 (0.89, 1.09)	1.01 (0.95, 1.08)	1.07 (0.93, 1.23)	1.03 (0.95, 1.11)
Heavy truck traffic (current)	0.90 (0.78, 1.04)	0.93 (0.87, 1.01)	1.08 (0.98, 1.19)	1.01 (0.96, 1.08)	1.07 (0.93, 1.23)	1.08 (1.01, 1.15)
Fast food (current)	0.92 (0.80, 1.06)	1.03 (0.95, 1.11)	1.01 (0.91, 1.11)	1.02 (0.96, 1.08)	1.07 (0.93, 1.23)	0.99 (0.92, 1.06)
Television (current)	1.08 (0.85, 1.38)	0.96 (0.85, 1.08)	0.92 (0.77, 1.08)	0.95 (0.87, 1.04)	1.03 (0.81, 1.29)	1.05 (0.94, 1.17)
Paternal tobacco (current)	1.06 (0.92, 1.24)	0.93 (0.86, 1.01)	0.90 (0.81, 1.00)	1.03 (0.96, 1.09)	1.04 (0.90, 1.21)	1.04 (0.97, 1.12)
Maternal tobacco (current)	1.30 (1.11, 1.53)	1.09 (0.98, 1.21)	0.83 (0.74, 0.93)	0.92 (0.85, 1.00)	0.92 (0.79, 1.09)	0.99 (0.90, 1.09)
Paracetamol (current)	1.29 (1.10, 1.51)	1.15 (1.06, 1.24)	0.97 (0.87, 1.08)	0.98 (0.92, 1.05)	0.79 (0.68, 0.92)	0.87 (0.81, 0.94)
Open fire cooking (current)	0.77 (0.41, 1.45)	0.92 (0.76, 1.11)	0.73 (0.45, 1.19)	0.97 (0.84, 1.13)	1.87 (0.97, 3.59)	1.20 (1.01, 1.44)

[A]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

Figure S1. Synthesis sample data flowchart, age 6-7 years

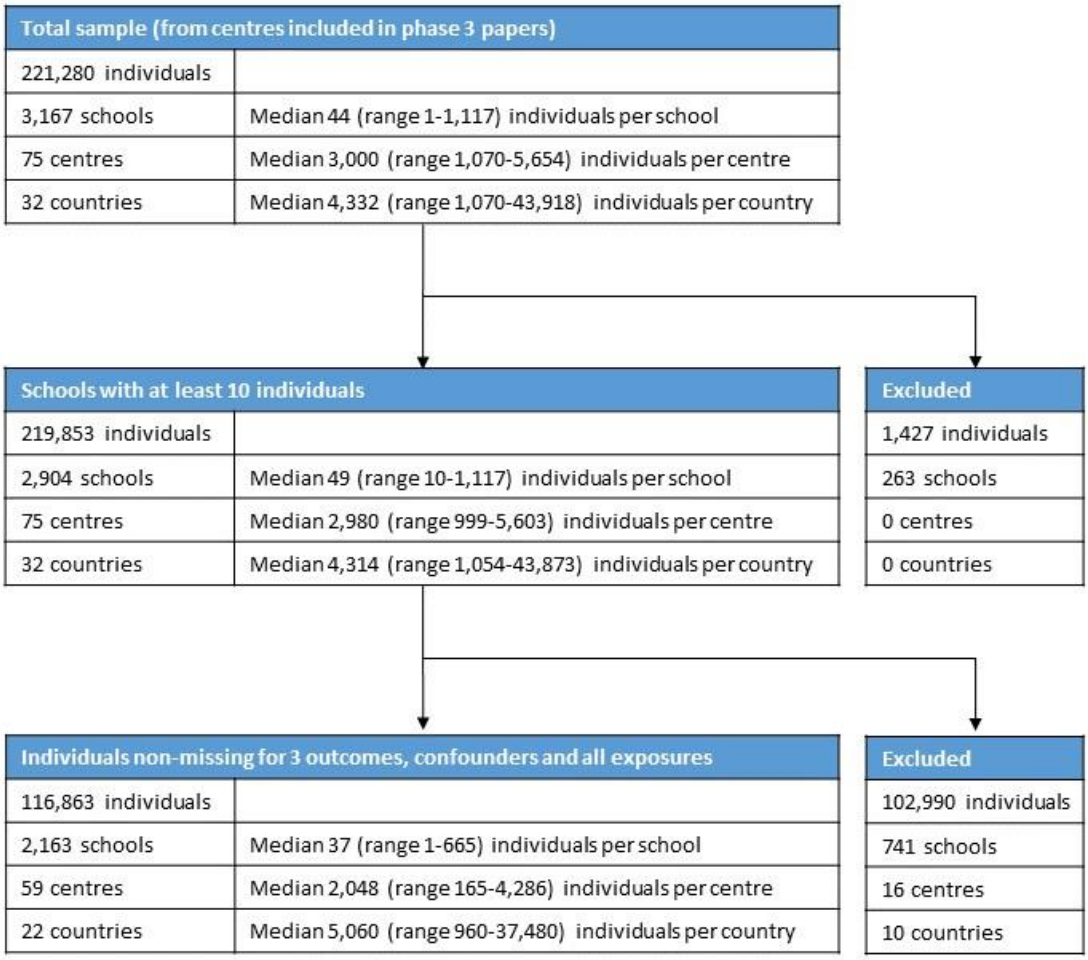

Figure S1 shows the data flow through the exclusions to the final analysed sample for the 6-7 year-old children.

Figure S2. Synthesis sample data flowchart, age 13-14 years

Total sample (from centres included in phase 3 papers)	
362,048 individuals	
2,592 schools	Median 100 (range 1-1,169) individuals per school
122 centres	Median 3,022 (range 66-7,384) individuals per centre
54 countries	Median 3,632 (range 66-46,053) individuals per country

Schools with at least 10 individuals		Excluded
361,750 individuals		298 individuals
2,528 schools	Median 103 (range 13-1,169) individuals per school	64 schools
122 centres	Median 3,020 (range 66-7,384) individuals per centre	0 centres
54 countries	Median 3,632 (range 66-45,984) individuals per country	0 countries

Individuals non-missing for 3 outcomes, confounders and all exposures		Excluded
224,436 individuals		137,314 individuals
2,037 schools	Median 80 (range 1-955) individuals per school	491 schools
97 centres	Median 2,490 (range 114-5,765) individuals per centre	25 centres
41 countries	Median 4,321 (range 1,664-39,055) individuals per country	13 countries

Figure S2 shows the data flow through the exclusions to the final analysed sample for the 13-14 year-old adolescents.

Figure S3. Triangular graphs showing unimorbid two-way comparisons of early life risk factor effects for 6-7-year-old children.

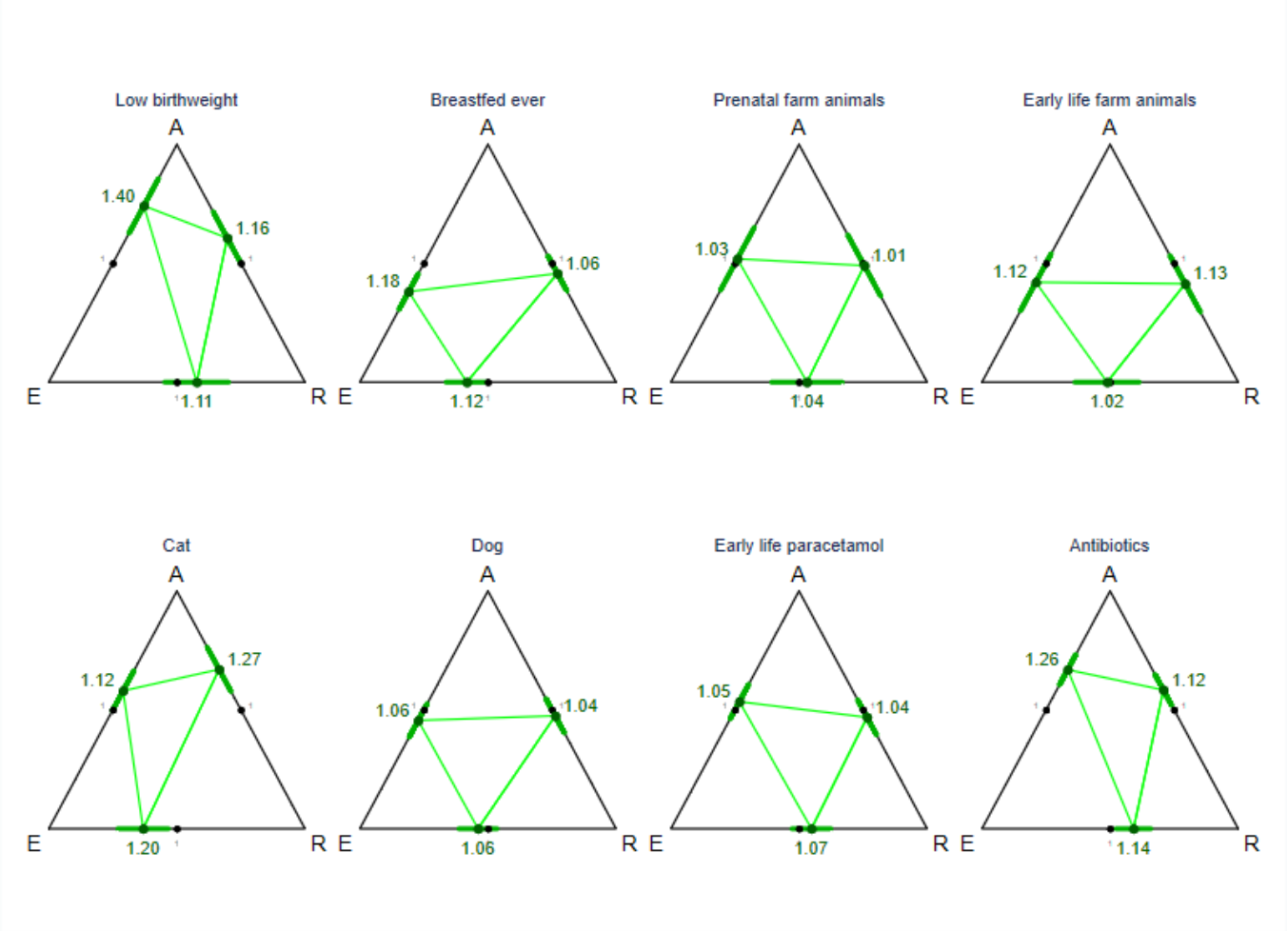

Figure S3: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Early life risk factors in 6-7 year-old children includes factors from the first year of the child's life (except prenatal farm animals which is mother's contact with farm animals during pregnancy with the child). The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.

Figure S4. Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 6-7-year-old children.

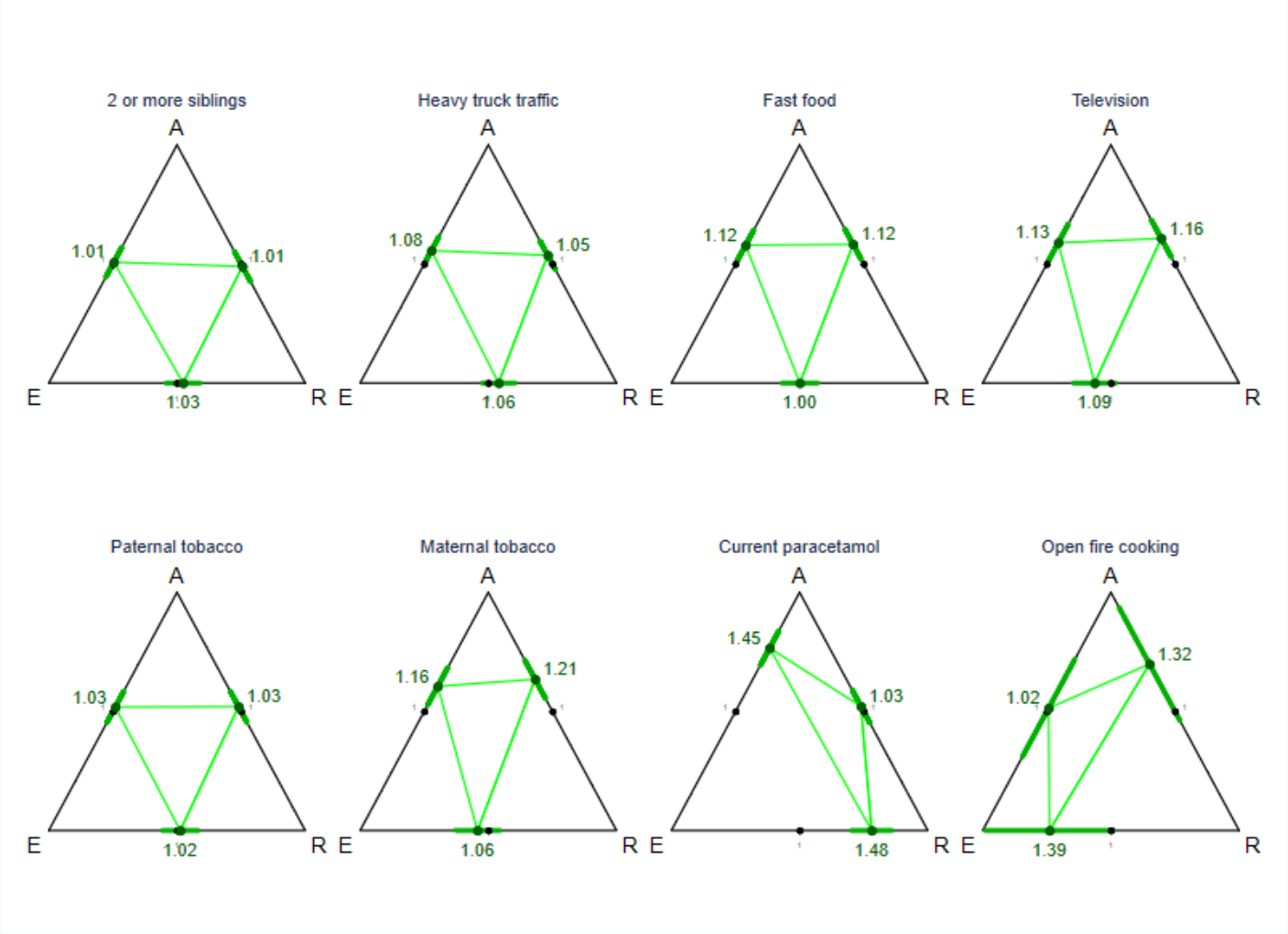

Figure S4: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 6-7 year-old children includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.

Figure S5. Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 13-14-year-old adolescents.

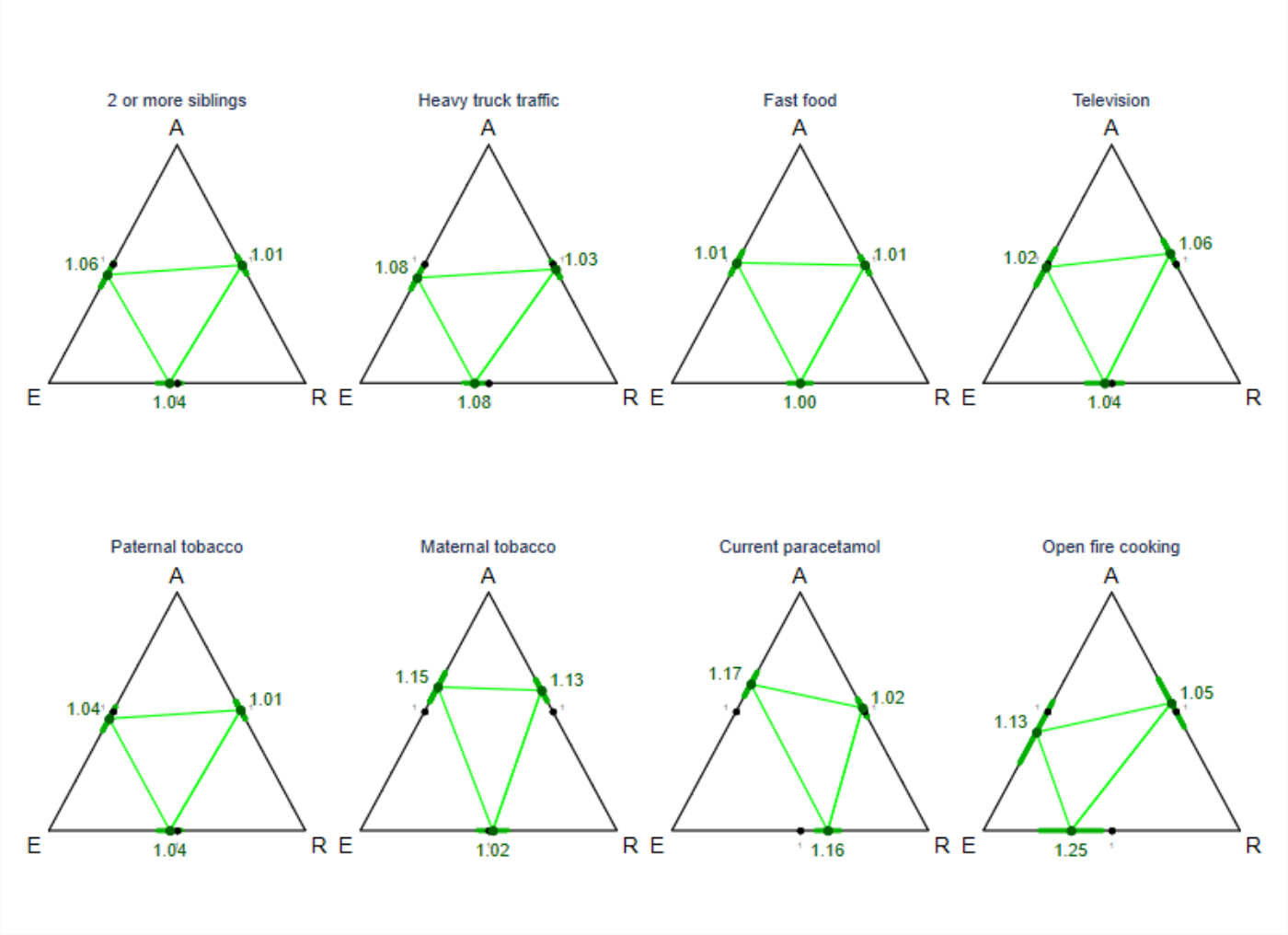

Figure S5: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 13-14 year-old adolescents includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.

Figure S6. Triangular graphs showing unimorbid two-way comparisons of effects of early life risk factors for 6-7-year-old children in affluent and non-affluent countries.

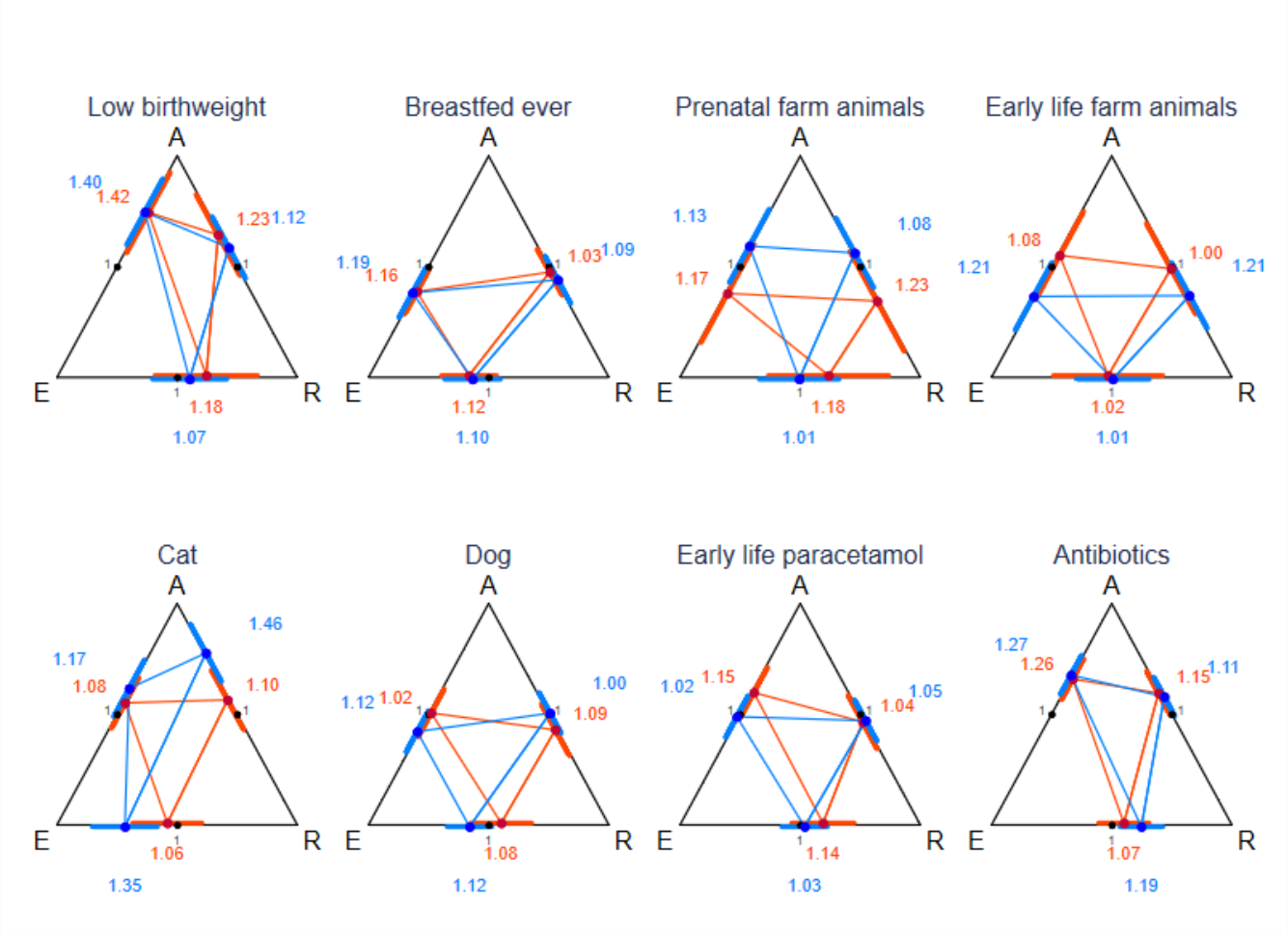

Figure S6: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Early life risk factors in 6-7 year-old children includes factors from the first year of the child's life (except prenatal farm animals which is mother's contact with farm animals during pregnancy with the child). The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.

Figure S7. Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 6-7-year-old children in affluent and non-affluent countries.

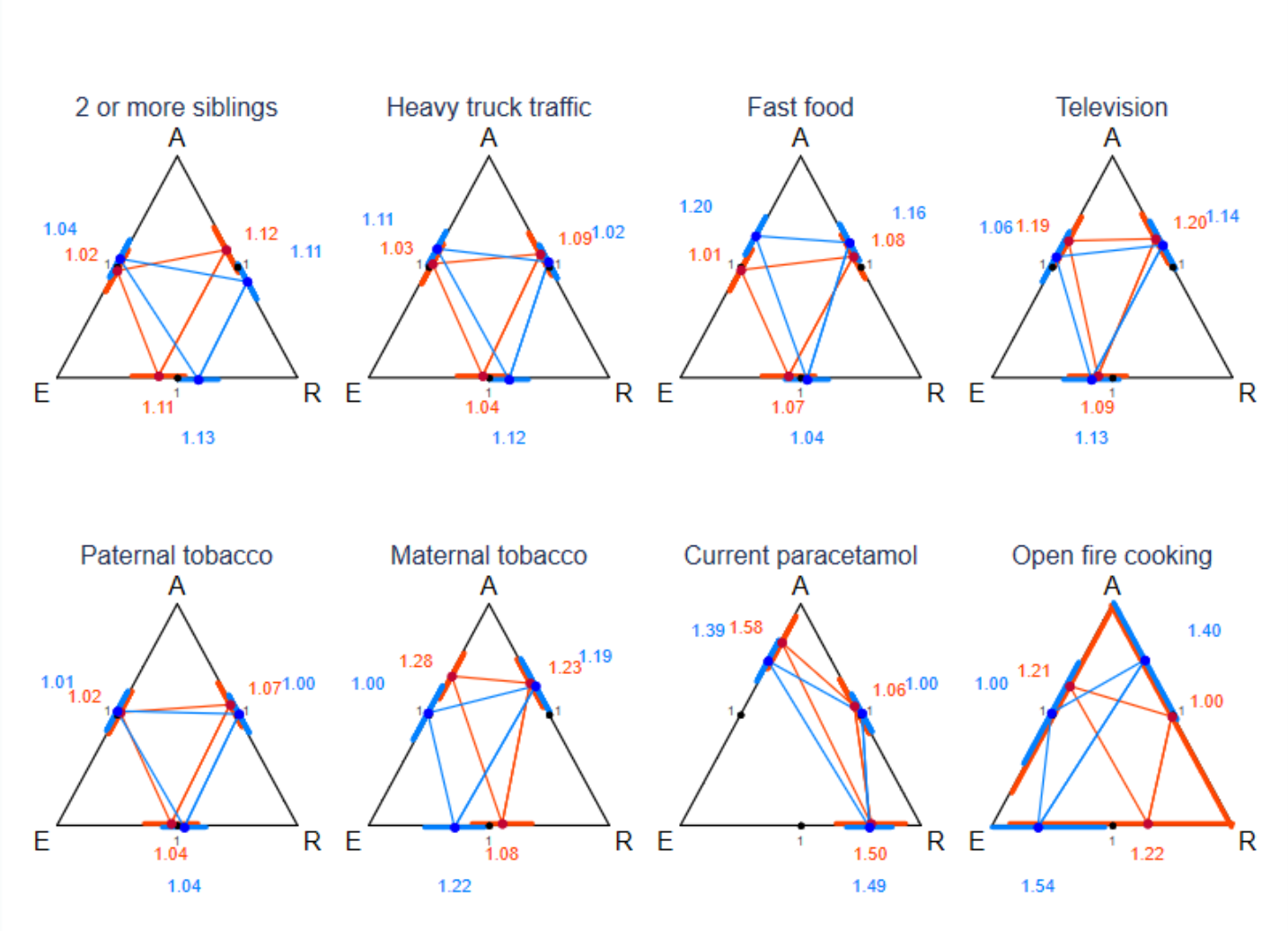

Figure S7: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 6-7 year-old children includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.

Figure S8. Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 13-14-year-old adolescents in affluent and non-affluent countries.

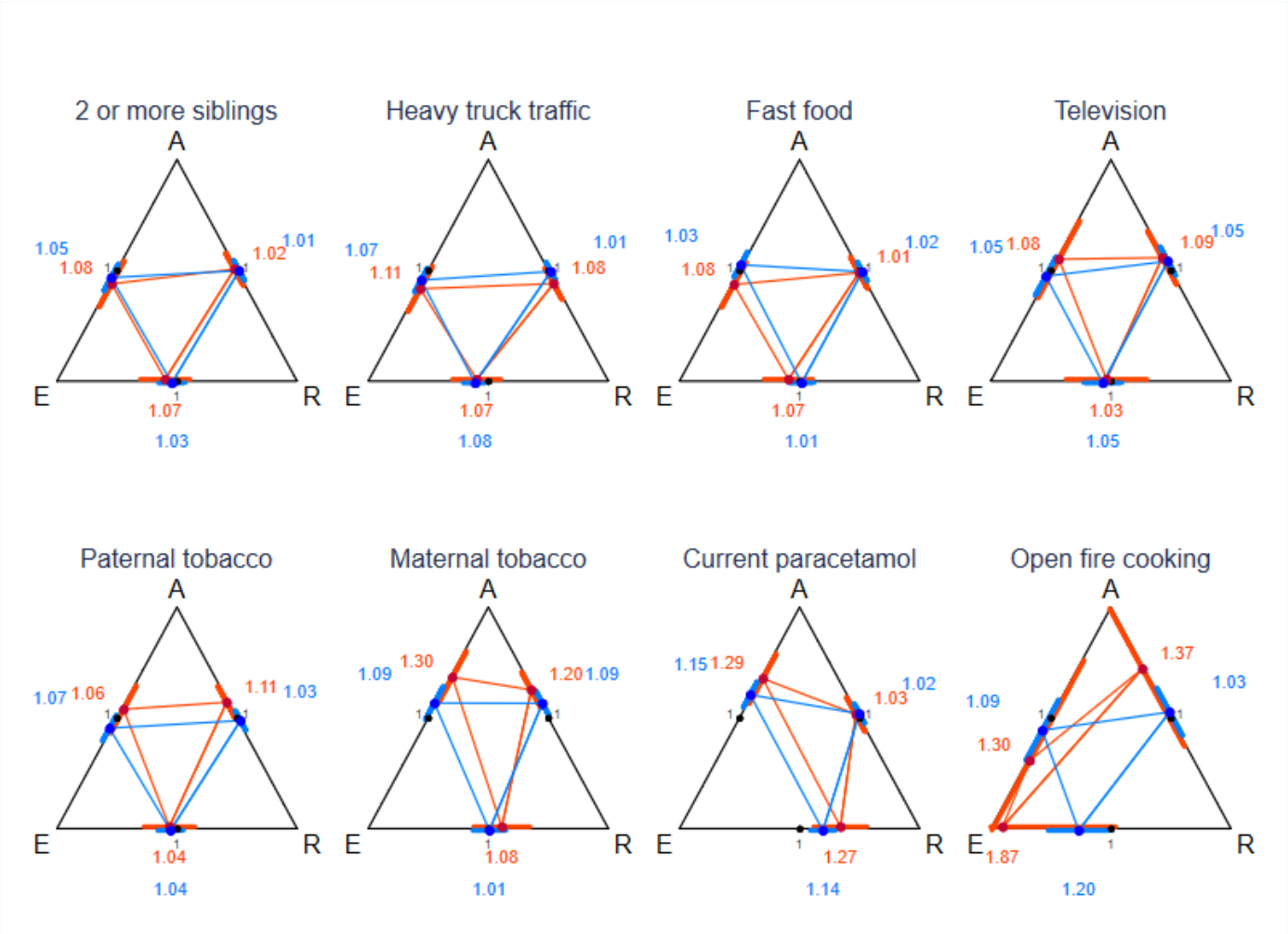

Figure S8: Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 13-14 year-old adolescents includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.