Are environmental factors for atopic eczema in ISAAC Phase Three due to reverse causation?

Short title: ISAAC: Risk factors for atopic eczema

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Abbreviations

ISAAC International Study of Asthma and Allergies in Childhood

OR Odds ratio

CI Confidence interval

FE Fixed effects

GNI Gross national income

CIA Central Intelligence Agency

ABSTRACT

Some previously described environmental associations for atopic eczema (AE) may be due to reverse causation. We explored the role of reverse causation by comparing individual- and school-level results for multiple AE risk factors.

ISAAC Phase Three surveyed children within schools (the sampling unit) on AE symptoms and potential risk factors. We assessed the effect of these risk factors on AE symptoms using mixed-effect logistic regression models, first with individual-level exposure data and second with school-level exposure prevalence.

546,348 children from 53 countries were included. At age 6-7 the strongest individual-level associations were with current paracetamol use (odds ratio=1.45, 95% confidence interval 1.37-1.54), which persisted at school-level (1.55, 1.10-2.21), antibiotics (1.41, 1.34-1.48) and early life paracetamol use (1.28, 1.21-1.36) with the former persisting at school-level while the latter was no longer observed (1.35, 1.00-1.82 and 0.94, 0.69-1.28 respectively). At age 13-14 the strongest associations at individual-level were with current paracetamol use (1.57, 1.51-1.63) and open-fire cooking (1.46, 1.33-1.62); both were stronger at school-level (2.57, 1.84-3.59 and 2.38, 1.52-3.73 respectively). Association with exposure to heavy traffic (1.31, 1.27-1.36) also persisted at school-level (1.40, 1.07-1.82).

Most individual- and school level effects were consistent tending to exclude reverse causation.

INTRODUCTION

Atopic eczema (AE) prevalence has increased substantially over the last 30 years; up to 20% of children in affluent westernized countries have AE during their lives and prevalence in low-and-middle income countries is increasing (Odhiambo et al., 2009). AE can have a major impact on sufferers and their families (Balkrishnan et al., 2003, Beattie and Lewis-Jones, 2006).

While genetic factors clearly play an important role in AE aetiology, the dramatic increase in prevalence of AE in low- and middle-income countries is not consistent with a major role of genetic factors (since these do not change rapidly over time), and strongly suggests that environmental factors are important (Odhiambo et al., 2009, Sandilands et al., 2006).

Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) has contributed significantly to understanding the associations between single environmental exposures and asthma, AE and rhinitis (Asher et al., 2010). However, environmental factors may confound each other's effects in allergic diseases; hence assessing the role of many key environmental factors together is useful. Findings of cross-sectional studies, including ISAAC, may be limited by reverse causation, where the direction of cause-and-effect is contrary to a common presumption. This arises when a child being at risk of or having AE has led to changes in environmental exposures. For example, parents may remove pets following AE onset if they believe pets exacerbate AE symptoms, resulting in a paradoxical association between increased pet exposure and decreased AE when measured at a single time point (Brunekreef et al., 2012a, Langan et al., 2007), rather than increased pet exposure increasing AE risk. Cross-sectional studies may also be limited by confounding by indication where the association with the risk factor has an alternative explanation; for example, AE may be complicated by skin infections requiring antibiotic treatment, leading to an observed

increased association between AE and antibiotic use, rather than antibiotics being on the causal pathway for AE. Confounding by indication has been considered as an alternative explanation in relation to paracetamol (acetaminophen) use and asthma aetiology (but not AE) in previous ISAAC papers, although paracetamol may be taken for symptoms of severe skin and other infections associated with AE.(Beasley et al., 2008)

In this study, we assessed the effects of the all the key environmental variables previously each singly associated with AE in ISAAC at an individual-level, aiming to find which variables were the most important. The individuals in ISAAC were within schools (the sampling unit). Therefore, at the same time, we also incorporated average school-level exposure estimates (calculated from the individual-level data) to assess whether associations seen for these multiple variables at individual-level could be due to bias from reverse causation.

In standard individual-level exposure models the estimated effect (here an odds ratio [OR]) corresponding to the individual-level risk factor can be interpreted as the OR of the exposed compared to the unexposed child, after adjustment for school-level prevalence (as a random intercept). This means bias due to reverse causation may be a concern where this is plausible, but the estimated effects will not be confounded by unmeasured ecological factors (other environmental factors affecting the whole population).

In school-level exposure prevalence models, the estimated OR corresponding to the school-level prevalence of the risk factor can be interpreted as the effect on an individual of attending a hypothetical school where all children are exposed compared to a hypothetical school where no children are exposed. School-level analyses can suffer from ecological bias, but there is less concern about reverse causation as the actions of a few parents will not significantly affect the school-level prevalence of an exposure. Therefore, comparing the

results of these models enables exploration of whether single individual-level risk factors, which could plausibly be due to reverse causation, persist or diminish when explored at school-level.

The complementary approach of individual- and school-level analyses used in this paper enables exploration of mutual confounding by environmental factors and different forms of reverse causation, including avoidance bias and confounding by indication.

RESULTS

6-7 year olds

The 6-7 year old sample contained 221,280 children (from 3,167 schools, 75 centres, 32 countries). There were 120,799 children (from 2,165 schools, 59 centres, 22 countries) with complete data across all analysis variables. See the data flowchart (Figure 1) for further details. Individual- and school-level summary statistics are presented in Table 1 for the "common sample" and Table S1 (Supplementary Material) for the "maximum sample" (see "Statistical analyses" section for definitions).

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 2 and S3). The strongest associations in the fully-adjusted individual-level analyses were for current paracetamol use (odds ratio (OR) = 1.45, 95%CI 1.37-1.54), antibiotic use in the first year of life (1.41, 1.34-1.48), and paracetamol use in the first year of life (1.28, 1.21-1.36) (Table 2).

In fully-adjusted school-level analyses, the associations for current paracetamol use (1.55, 1.10-2.21) and early life antibiotic use (1.35, 1.00-1.82) were maintained, but the association with early life paracetamol use disappeared (0.94, 0.69-1.28) (Table 2). Stronger associations were observed at school-level for open fire cooking (1.84, 0.98-3.45 compared to 1.12, 0.95-1.32 at individual-level), and maternal tobacco use (1.61, 1.14-2.25 compared to 1.06, 0.99-1.13 at individual-level). A weak association with current heavy traffic exposure observed at individual-level was no longer significant at school level. Associations with breastfeeding were similar in individual and school-level analyses (1.11, 1.05-1.18 and 1.06, 0.75-1.48) but with less precision. A potentially harmful association of low birthweight with AE symptoms was seen at school-level (1.78, 1.07-2.95) compared to a small protective association at individual-level (0.89, 0.81-0.97) (Table 2).

In analyses stratified by country-level affluence (Tables S4-S5, Supplementary Material), there was strong evidence at individual-level that being exposed to a cat, dog or farm animals in the first year of life, or maternal contact with farm animals while pregnant, was associated with AE symptoms in non-affluent countries at individual level (Tables S4 and S5), while none of these associations were observed at school-level in either setting. There was also evidence that the association of AE symptoms with current paracetamol was strong at individual and school-level with stronger estimates in affluent countries (1.64; 1.49-1.79) than non-affluent settings (1.35, 1.25-1.45). Weak associations with breastfeeding were only observed at individual-level in affluent countries, but were not observed at school-level, with no association being seen in non-affluent countries.

13-14 year olds

The full 13-14 year old sample contained 362,048 adolescents (from 2,592 schools, 122 centres, 54 countries). There were 233,159 adolescents (from 2,039 schools, 97 centres, 41 countries) with complete data across all analysis variables. See the data flowchart (Fig. 2) for further details. Individual- and school-level summary statistics are presented in Table 1 for the common sample and Table S1 (Supplementary Material) for the maximum sample.

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 2 and S3). The strongest associations in fully-adjusted individual-level analyses were for current paracetamol use (1.57, 1.51-1.63), cooking on an open fire (1.46, 1.33-1.62), and exposure to heavy truck traffic (1.31, 1.27-1.36) (Table 2).

In fully-adjusted school-level analyses associations for current paracetamol use (2.57, 1.84-3.59), cooking on an open fire (2.38, 1.52-3.73) and heavy truck traffic (1.40, 1.07-1.82) were maintained (Table 2). An association was also observed at school-level for fast food consumption (2.11, 1.66-2.70) with a much weaker association at individual-level (1.05,

1.02-1.10). At individual-level there was an association with paternal tobacco use (1.15, 1.10-1.19), with conflicting findings at school-level (0.64, 0.44-0.94).

In analyses stratified by country-level affluence (Tables S4-S5, Supplementary Material) there was evidence at individual-level that current paracetamol use was slightly more strongly associated with AE symptoms in affluent (1.75, 1.60-1.92) than non-affluent (1.53, 1.47-1.60) countries (Table S4), with stronger associations in both settings at school-level (Table S5). There was also some evidence that paternal tobacco use was associated with AE symptoms in non-affluent countries (1.17, 1.12-1.23) at individual-level, but not at school-level, and no association was seen in affluent settings (1.05, 0.96-1.14).

DISCUSSION

This study is the first comprehensive analysis of key risk factors for childhood AE, analysed together in a multivariable regression analysis, at individual (child) level to find which variables were the most important, and community (school) level to find which ones remained important. The school was the sampling unit, so analyses using school-level prevalence of exposures offer novel insights into the possible extent of bias due selective avoidance or confounding by indication. These forms of reverse causation, which are a particular issue in cross-sectional analyses, are less of an issue using school-level exposures rather than individual-level exposures. When comparing school-level and individual-level findings, if confounding by indication was a major issue, associations would be weaker at school-level, whereas if selective avoidance was the source of reverse causation, associations at the school-level would appear more harmful. Consistent findings between school and individual-level analyses suggest that neither of the two forms of reverse causation explain the findings. In contrast, school-level analyses are prone to ecologic (population level) confounding, which is not an issue when using the individual-level approach. Given that the individual- and school-level analyses will potentially be affected in different ways by reverse causation and confounding by indication, we consider it is sensible to fit regression models at each level (child within school and school within centre) and compare the results to assess robustness to different interpretations, rather than considering one approach more appropriate than the other. The analyses use the data from ISAAC Phase Three, where many individual-level single risk factor analyses found associations, but some of these were not corroborated in the present analyses.

6-7 year olds

The 6-7 year old results from the present study are summarised and compared with previous ISAAC analyses in Table 3, along with an assessment of potential bias and an outline of the biological plausibility of the effect.

The strongest associations for 6-7 year olds in individual-level analyses were for current paracetamol use, and antibiotic and paracetamol use in the first year of life. However in school-level analyses, only associations with current paracetamol persisted. These school-level findings provide evidence against reverse causation, including confounding by indication, as an explanation, and thus make a causal link more likely. Associations between AE and current paracetamol use are consistent with those from individual-level single risk factor analyses in previous ISAAC Phase Three publications, which reported dose-response relationships between the quantity of paracetamol taken in the previous year and current AE symptoms (medium 1.18 (1.08-1.30) and high 1.87 (1.68-2.08) compared to no paracetamol) (Beasley et al., 2008). Possible biological mechanisms underlying the observed association between paracetamol use and AE may relate to a depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to a predominantly Th2 immune response. (Beasley et al., 2008, Beasley et al., 2011, Peterson et al., 1998)

Associations with early antibiotic use persisted after adjusting for confounders and were also observed in school-level analyses, although this association was weaker, suggesting that confounding by indication may partly contribute to the association, but does not completely explain it. Findings are consistent with those observed in individual-level single risk factor analyses (1.42 (1.33-1.51)) in previous ISAAC Phase Three publications (Foliaki et al., 2009). In our further analyses, stratifying by affluence, similar associations with early antibiotic use were observed in affluent and non-affluent countries. The reasons for this association with antibiotics and potential causality are unclear, with proposed theories including changes in the gut microbiome.(Tsakok et al., 2013)

Breastfeeding was associated with a slightly increased risk of AE at individual-level with similar but weaker results at school-level. The individual-level association was strongest in affluent countries but was not significant at school level (Tables S4 and S5). These observations reflect previous reports when assessing breastfeeding as an individual-level exposure in ISAAC Phase Three data (1.05, 0.97-1.12) (Bjorksten et al., 2011). Our findings do not support the reverse causation theory that in affluent countries those children at highest risk of developing AE are more likely to be breastfed (Bjorksten et al., 2011, Yang et al., 2009).

We observed evidence of a weak protective effect of low birthweight in individual-level analyses in contrast to a potentially harmful effect in school-level analyses. Individual-level findings are consistent with the previous ISAAC individual-level single risk factor analyses; although additionally these analyses showed no association between birthweight and AE severity and the importance of the finding from a public health perspective was not clear (Mitchell et al., 2014). It is possible that the opposite school-level association may indicate residual socio-economic confounding at community level as schools with a high proportion of low birthweight children may be in more deprived areas (Dibben et al., 2006).

We also observed weak evidence in individual-level analyses that current AE was slightly more common in children exposed to cats, dogs and farm animals in the first year of life. There were similar results at school-level. In stratified analyses all of these associations were restricted only to non-affluent settings, where there is likely to be less awareness of these associations with AE, making bias or differential recall of exposure less likely explanations. Findings for these combined analyses of the ISAAC Phase Three data are consistent with those observed in individual-level single risk factor analyses (Brunekreef et al., 2012a, Brunekreef et al., 2012b).

Current heavy traffic exposure was associated with a weak increased risk of AE symptoms in individual-level but not school-level analyses. A possible explanation for the differential associations at individual-level and school-level relates to bias; perhaps parents of individuals with current AE symptoms are more concerned about heavy traffic exposure and more likely to report it compared to those without symptoms. These findings may help interpret the similar associations observed in previous individual-level single risk factor analyses (Brunekreef et al., 2009).

13-14 year olds

The 13-14 year old results from the present study are summarised and compared with previous ISAAC analyses in Table 4, along with an assessment of potential bias and an outline of the biological plausibility of the effect.

The strongest association with current AE in adolescents at individual-level was with current paracetamol use, with even stronger potentially harmful associations observed at school-level. The stronger school-level associations suggest that reverse causation is unlikely to explain these associations, although ecological confounding, whereby confounding arises due to within-area heterogeneity of exposures, is possible. Findings are consistent with previous individual-level single risk factors analyses (Beasley et al., 2011).

Using open fires for cooking was more strongly associated with current AE symptoms at school-level compared to individual-level, findings which could be partially attributed to avoidance behaviour in parents of children with current AE (Wong et al., 2013). The association with AE observed at individual-level at age 13-14 years with no association at age 6-7 years is consistent with previous single exposure ISAAC studies.(Wong et al., 2013)

Strong potentially harmful associations with AE symptoms were seen for current heavy traffic exposure at individual-level and school-level. This is in contrast to the younger age-group; a possible explanation is that persistent AE may be more severe and more likely to react to aeroallergens and irritants. Individual-level analyses demonstrated similar associations with a dose-response relationship between levels of exposure to traffic and AE symptoms.(Brunekreef et al., 2009)

Though weak associations were observed at individual-level with current maternal and paternal tobacco exposure, at school-level the effect was reversed with weak evidence of a protective effect for paternal smoking. This finding might support differential reporting of tobacco exposure in those with current AE symptoms or ecologic bias at school level (Mitchell et al., 2012).

Strong associations were observed at school-level with fast food consumption, with very weak associations being observed at individual-level. Findings are consistent with previous individual-level single risk factor analyses and might plausibly be important for the aetiology of AE, although ecologic bias and residual confounding are alternative possibilities (Ellwood et al., 2001, Ellwood et al., 2013).

Weak associations were observed between having two or more siblings and current AE symptoms at an individual-level with slightly stronger associations at school-level (but with weaker precision). Findings are not consistent with those observed at age 6-7 years of age, are in contrast to protective associations reported in individual-level single risk factor analyses, and may represent a chance association (Strachan et al., 2015).

Strengths and limitations of the study

The ISAAC study had worldwide coverage and a very large sample size, including countries from less affluent settings, thus facilitating the study of environmental factors in varied settings (Odhiambo et al., 2009). The use of standardised and validated methods of symptoms reporting is a particular strength of the ISAAC study (Flohr et al., 2009). Although self-reported symptoms may be prone to misclassification, they avoid major diagnostic differences due to access to care in different countries and settings, where relying on doctor diagnosis may be more problematic. Selection bias is an unlikely explanation for the findings as response rates of the children were high (85%).

Assessment of exposures was based on parental or guardian (6-7 year old children) and study participant (13-14 year old adolescents) completion of questionnaires about historical exposures rather than objective measures, leading to possible misclassification, which for different exposures may be non-differential or may be prone to recall biases or reverse causation. Schools were the sampling unit, with individual children of the age group responding within the school, and this structure of the cross-sectional survey enabled these analyses.

Both individual-level and school-level analyses may be biased by residual confounding by factors that were either imperfectly measured or not measured at all; however, as the unmeasured confounders are likely to be different at school and individual level, consistency of findings at both levels is reassuring against associations being due to residual confounding.

Conclusions

We have further enhanced the ISAAC analyses by using school-level as well as individual-level exposures, thus allowing us to explore whether specific findings may be due to reverse causation, including confounding by indication. Despite plausible mechanisms, we did not observe findings supportive of selective avoidance in relation to furry pet exposure. The

consistent associations between current paracetamol exposure in both age groups and at both individual and school-level argues against reverse causation as the sole explanation. The consistent associations between current paracetamol exposure in both age groups and at both individual and school-level argues against reverse causation as the sole explanation. If paracetamol use in early childhood does have a direct biological role in the development of atopic eczema and related disorders such as asthma, then reducing paracetamol use in infancy could reduce the incidence of such diseases. Indeed, a randomised controlled prevention trial in New Zealand called PIPPA Tamariki (ACTRN12618000303246) that seeks to determine whether ibuprofen instead of paracetamol for fever/pain in infancy reduces the incidence of asthma and eczema, is already underway.

Some individual-level single risk factor associations previously identified in ISAAC Phase Three data were not corroborated in the present analyses, but several were: current paracetamol use at ages 6-7 and 13-14, early life antibiotic exposure and AE at age 6-7, and current heavy road traffic and open fire cooking and AE symptoms at 13-14 years. The novel approach of using school-level exposure estimates provides insight that some of the previously reported associations in ISAAC Phase Three studies may be due to reverse causation, but that paracetamol use is unlikely to be explained in this way.

MATERIAL AND METHODS

Study

A detailed description of the ISAAC Phase Three methods can be found elsewhere (Ellwood et al., 2005), and they will be briefly summarized here. ISAAC Phase Three is a multi-centre, multi-country, cross-sectional study of two age groups of schoolchildren (6-7 year old children and 13-14 year old adolescents) chosen from a random sample of schools in a defined geographical area (Asher et al., 1995). The Phase Three survey included a standardised symptom questionnaire, which obtained data on symptoms of asthma, rhinoconjunctivitis and AE (Asher et al., 1995). It also included a supplementary questionnaire which obtained data on a wide range of possible risk factors for the development of allergic disorders (Beasley et al., 2008). Parents or guardians completed the questionnaires for 6-7 year olds and 13-14 year olds answered the questionnaires themselves (http://isaac.auckland.ac.nz). Centre eligibility is described in the supplementary methods.

Variables

The outcome of interest, AE symptoms in the last 12 months, was defined by positive responses to the questions “Has your child/have you ever had an itchy rash which was coming and going for at least six months?”, “Has your child/have you had this itchy rash at any time in the last 12 months?” and “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?”.

Analyses in this paper included only the key environmental variables previously each singly associated with AE in ISAAC at an individual-level. Full definitions of the environmental risk factors are in Table S2 of the Supplementary Material.

Additionally, the analysis considered confounding by sex and highest level of maternal education (primary, secondary, tertiary, missing/not stated).

Finally, stratification by affluence of country was achieved using standard approaches (see Supplementary methods).

Statistical analyses

The two age groups were analysed separately. All analyses were conducted using mixed effect logistic regression models. There are four hierarchies of data in the study design: individual, school, centre and country. We accounted for this by including random intercepts at each of the higher 3 levels. Sex and highest level of maternal education were adjusted for as individual-level confounders in all models. The school-level prevalence of each risk factor was calculated as the proportion of children with that risk factor out of all children included in the analysis within that school.

Separate models were used to assess the effects of individual-level exposures and aggregated school-level prevalence of exposures on the individual-level outcome. Using the approach proposed by (Begg and Parides, 2003), these effects were formally compared within a multi-level framework, by fitting "hybrid fixed effect models". Results from these models were consistent with a simpler approach and are not discussed further.

Within each of these approaches, a minimally adjusted model was fitted. This was done on two samples (i) the "maximum sample" which was the sub-sample that had no data missing for AE, the confounders (sex, level of maternal education) and the one exposure of interest (ii) the "common sample" which was the sub-sample that had no data missing for AE, confounders and all exposures of interest. A fully adjusted model was also fitted to the common sample. Fully adjusted models included all risk factors at the individual level for the

individual-level models, school-level prevalence of all the risk factors for the school-level models.

The extent of co-linearity in fully adjusted models was examined by comparing the standard errors in the fully adjusted model with the standard errors in the minimally adjusted model (common sample). Fully adjusted analyses were additionally stratified by 'affluent' and 'non-affluent' countries to assess whether avoidance behaviour may have contributed to observed associations (since such behaviour is more likely in more affluent countries). Effect modification by country-level affluence was tested for each risk factor separately.

All analyses were conducted using Stata version 14.2 (StataCorp, 2015). Informed consent was obtained from parents of all participating children; the ISAAC Phase Three study was approved by local institutional review boards in all participating centres.

CONFLICT OF INTEREST

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REFERENCES

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. European Respiratory Journal 1995;8(3):483-91.

Asher MI, Stewart AW, Mallol J, Montefort S, Lai CK, Ait-Khaled N, et al. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of ISAAC Phase One. Respir Res 2010;11:8.

Balkrishnan R, Housman TS, Carroll C, Feldman SR, Fleischer AB. Disease severity and associated family impact in childhood atopic dermatitis. Arch Dis Child 2003;88(5):423-7.

Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet 2008;372(9643):1039-48.

Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, Mutius E, 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(2):171-8.

Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. Br J Dermatol 2006;155(6):1249-55.

Begg MD, Parides MK. Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. Stat Med 2003;22(16):2591-602.

Bjorksten B, Ait-Khaled N, Innes Asher M, Clayton TO, Robertson C, Group IPTS. 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 (Madr) 2011;39(6):318-25.

Brunekreef B, Stewart AW, Anderson HR, Lai CK, Strachan DP, Pearce N, 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(11):1791-8.

Brunekreef B, Von Mutius E, Wong G, Odhiambo J, Garcia-Marcos L, Foliaki S, et al. Exposure to cats and dogs, and symptoms of asthma, rhinoconjunctivitis, and eczema. Epidemiology 2012a;23(5):742-50.

Brunekreef B, Von Mutius E, Wong GK, Odhiambo JA, Clayton TO, Group IPTS. Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study. Int J Epidemiol 2012b;41(3):753-61.

Central Intelligence Agency. The World Factbook. www.cia.gov/library/publications/download/download-2002/2002.

Dibben C, Sigala M, Macfarlane A. Area deprivation, individual factors and low birth weight in England: is there evidence of an "area effect"? J Epidemiol Community Health 2006;60(12):1053-9.

Ellwood P, Asher MI, Beasley R, Clayton T, Stewart A, ISAAC Steering Committee. The International Study of Asthma and Allergies in Childhood (ISAAC): Phase Three rationale and methods. International Journal of Tuberculosis and Lung Disease 2005;9(1):10-6.

Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. Eur Respir J 2001;17(3):436-43.

Ellwood P, Asher MI, Garcia-Marcos L, Williams H, Keil U, Robertson C, 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(4):351-60.

Flohr C, Weinmayr G, Weiland SK, Addo-Yobo E, Annesi-Maesano I, Bjorksten B, et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. The British journal of dermatology 2009;161(4):846-53.

Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S, von Mutius E. 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. Journal of Allergy and Clinical Immunology 2009;124(5):982-9.

Langan S, Flohr C, Williams H. The role of furry pets in eczema: a systematic review. Arch Dermatol 2007;143(12):1570-7.

Mitchell EA, Beasley R, Keil U, Montefort S, Odhiambo J, Group IPTS. 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(11):941-9.

Mitchell EA, Clayton T, Garcia-Marcos L, Pearce N, Foliaki S, Wong G. Birthweight and the risk of atopic diseases: the ISAAC Phase III study. Pediatr Allergy Immunol 2014;25(3):264-70.

Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol 2009;124(6):1251-8.e23.

Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. Proc Natl Acad Sci U S A 1998;95(6):3071-6.

Sandilands A, O'Regan G, Liao H, Zhao Y, Terron-Kwiatkowski A, Watson R, et al. Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. J Invest Dermatol 2006;126(8):1770-5.

StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP2015.

Strachan DP, Ait-Khaled N, Foliaki S, Mallol J, Odhiambo J, Pearce N, 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(1):126-36.

The World Bank. GNI per capita, Atlas method (current US$), http://data.worldbank.org/indicator/NY.GNP.PCAP.CD; 2016a [accessed 24th Oct.2016].

The World Bank. World Bank GNI per capita Operational Guidelines and Analytical Classifications, http://siteresources.worldbank.org/DATASTATISTICS/Resources/OGHIST.xls; 2016b [accessed 1st Feb.2017].

Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. British Journal of Dermatology 2013;169(5):983-91.

Wong GW, Brunekreef B, Ellwood P, Anderson HR, Asher MI, Crane J, 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(5):386-94.

Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol 2009;161(2):373-83.

Table 1: Summary statistics in subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample").

Age group	Variable	Individual-level (n = 120,799)	School-level (n = 2,165)	
		Prevalence	Median prevalence	Prevalence IQR
6-7 years	AE in the last 12 months	0.074	0.064	(0.021, 0.120)
	Farm animals (in utero)	0.077	0.066	(0.023, 0.127)
	Low birthweight	0.077	0.056	(0.022, 0.097)
	Paracetamol (1st year)	0.662	0.707	(0.571, 0.843)
	Antibiotics (1st year)	0.557	0.571	(0.472, 0.654)
	Breastfed ever	0.805	0.837	(0.735, 0.918)
	Cat (1st year)	0.109	0.083	(0.036, 0.167)
	Dog (1st year)	0.198	0.197	(0.100, 0.307)
	Farm animals (1st year)	0.094	0.083	(0.037, 0.148)
	2 or more siblings	0.347	0.328	(0.185, 0.484)
	Heavy Truck traffic (current)	0.380	0.378	(0.270, 0.487)
	Fast food (current)	0.396	0.311	(0.165, 0.500)
	Paternal tobacco (current)	0.318	0.348	(0.211, 0.478)
	Maternal tobacco (current)	0.163	0.167	(0.044, 0.328)
	Paracetamol (current)	0.180	0.142	(0.061, 0.250)
	Open fire cooking (current)	0.019	0.000	(0.000, 0.016)
Age group	Variable	Individual-level (n = 233,159)	School-level (n = 2,039)	
		Prevalence	Median prevalence	Prevalence IQR
13-14 years	AE in the last 12 months	0.062	0.048	(0.022, 0.091)
	2 or more siblings	0.541	0.593	(0.377, 0.800)
	Heavy Truck traffic (current)	0.396	0.392	(0.301, 0.500)
	Fast food (current)	0.536	0.528	(0.391, 0.680)
	Paternal tobacco (current)	0.384	0.371	(0.238, 0.490)
	Maternal tobacco (current)	0.183	0.185	(0.036, 0.354)
	Paracetamol (current)	0.270	0.298	(0.177, 0.417)
	Open fire cooking (current)	0.052	0.006	(0.000, 0.029)

Table 2. Effects of individual- and school-level exposures on atopic eczema symptoms in the last 12 months in subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.

Age group	Exposure	Individual-level exposure		School-level exposure	
		Minimally adjusted[A]	Fully adjusted[B]	Minimally adjusted[A]	Fully adjusted[B]
6-7 years (n = 120,799)	Farm animals (in utero)	1.32 (1.22, 1.43)	1.11 (1.00, 1.23)	1.48 (1.04, 2.12)	1.05 (0.54, 2.04)
	Low birthweight	0.92 (0.84, 1.01)	0.89 (0.81, 0.97)	2.32 (1.43, 3.76)	1.78 (1.07, 2.95)
	Paracetamol (1st year)	1.53 (1.45, 1.61)	1.28 (1.21, 1.36)	1.11 (0.85, 1.46)	0.94 (0.69, 1.28)
	Antibiotics (1st year)	1.56 (1.49, 1.64)	1.41 (1.34, 1.48)	1.32 (1.00, 1.75)	1.35 (1.00, 1.82)
	Breastfed ever	1.09 (1.03, 1.16)	1.11 (1.05, 1.18)	0.97 (0.69, 1.35)	1.06 (0.75, 1.48)
	Cat (1st year)	1.17 (1.10, 1.25)	1.10 (1.03, 1.17)	1.40 (0.99, 1.97)	1.15 (0.78, 1.71)
	Dog (1st year)	1.12 (1.07, 1.18)	1.05 (1.00, 1.11)	1.20 (0.90, 1.61)	0.96 (0.69, 1.32)
	Farm animals (1st year)	1.32 (1.23, 1.42)	1.16 (1.06, 1.27)	1.50 (1.07, 2.10)	1.15 (0.62, 2.15)
	2 or more siblings	0.96 (0.91, 1.01)	0.95 (0.90, 0.99)	1.26 (1.01, 1.56)	1.11 (0.88, 1.40)
	Heavy Truck traffic (current)	1.16 (1.11, 1.22)	1.11 (1.06, 1.16)	0.92 (0.74, 1.14)	0.81 (0.65, 1.02)
	Fast food (current)	1.03 (0.98, 1.08)	0.99 (0.94, 1.04)	0.94 (0.75, 1.18)	0.96 (0.76, 1.22)
	Paternal tobacco (current)	1.08 (1.03, 1.13)	1.04 (0.99, 1.10)	1.18 (0.92, 1.53)	0.83 (0.61, 1.13)
	Maternal tobacco (current)	1.10 (1.04, 1.17)	1.06 (0.99, 1.13)	1.56 (1.18, 2.07)	1.61 (1.14, 2.25)
	Paracetamol (current)	1.60 (1.51, 1.69)	1.45 (1.37, 1.54)	1.63 (1.17, 2.26)	1.55 (1.10, 2.21)
	Open fire cooking (current)	1.15 (0.97, 1.35)	1.12 (0.95, 1.32)	2.30 (1.27, 4.16)	1.84 (0.98, 3.45)
Age group	Exposure	Individual-level exposure		School-level exposure	
		Minimally adjusted[A]	Fully adjusted[B]	Minimally adjusted[A]	Fully adjusted[B]
13-14 years (n = 233,159)	2 or more siblings	1.10 (1.05, 1.14)	1.08 (1.03, 1.12)	1.34 (1.04, 1.74)	1.26 (0.97, 1.65)
	Heavy Truck traffic (current)	1.36 (1.31, 1.41)	1.31 (1.27, 1.36)	1.66 (1.28, 2.17)	1.40 (1.07, 1.82)
	Fast food (current)	1.10 (1.05, 1.14)	1.05 (1.02, 1.10)	2.08 (1.63, 2.66)	2.11 (1.66, 2.70)
	Paternal tobacco (current)	1.21 (1.16, 1.25)	1.15 (1.10, 1.19)	0.85 (0.61, 1.17)	0.64 (0.44, 0.94)
	Maternal tobacco (current)	1.19 (1.14, 1.25)	1.11 (1.06, 1.16)	0.72 (0.50, 1.04)	0.79 (0.52, 1.19)
	Paracetamol (current)	1.61 (1.55, 1.67)	1.57 (1.51, 1.63)	2.68 (1.91, 3.75)	2.57 (1.84, 3.59)
	Open fire cooking (current)	1.47 (1.33, 1.62)	1.46 (1.33, 1.62)	2.29 (1.47, 3.57)	2.38 (1.52, 3.73)

[A]Adjusted for sex and mothers level of education. [B]Additionally adjusted for all other variables in the table.

Table 3. Associations between eczema symptoms in the last 12 months and risk factors for 6-7 year old age group comparing results from different analyses

Exposure	Current analysis			Previous ISAAC analysis		Assessment of bias	Biological plausibility of effect
	Individual	School level[b]	Comparison	Individual level[c]	Comparison with current analysis		
Farm animals (in utero)	1.11 (1.00, 1.23)	1.05 (0.54, 2.04)	No association at school level	1.17 (1.07,1.29) (Brunekreef et al., 2012b)	Consistent	No evidence of reverse causation bias	Not observed at school level
Low birthweight	0.89 (0.81, 0.97)	1.78 (1.07, 2.95)	Individual shows a protective effect but school level is harmful	0.93 (0.85, 1.01) (Mitchell et al., 2014)	Consistent with current individual level estimate	There could be SES confounding at community level	Unclear
Paracetamol (1st year)	1.28 (1.21, 1.36)	0.94 (0.69, 1.28)	The significantly harmful effect seen at the individual level doesn't show at the school-level	1.35 (1.26, 1.45) (Beasley et al., 2008)	Consistent with current individual level estimate	Possible evidence of reverse causation	Unclear
Antibiotics (1st year)	1.41 (1.34, 1.48)	1.35 (1.00, 1.82)	Consistent but weaker	1.42 (1.33,1.51) (Foliaki et al., 2009)	Consistent	Confounding by indication may partly contribute to the association.	Confounding by indication may contribute
Breastfed ever	1.11 (1.05, 1.18)	1.06 (0.75, 1.48)	Consistent but weaker	1.05 (0.97,1.12) (Bjorksten et al., 2011)	Consistent	No evidence of reverse causation bias	Weak association; biological basis not clear

Cat (1st year)	1.10 (1.03, 1.17)	1.15 (0.78, 1.71)	Consistent	1.09 (1.01,1.17) (Brunekreef et al., 2012a)	Consistent	No evidence of reverse causation bias	-
Dog (1st year)	1.05 (1.00, 1.11)	0.96 (0.69, 1.32)	Consistent	Not available	N/A	No evidence of effect	-
Farm animals (1st year)	1.16 (1.06, 1.27)	1.15 (0.62, 2.15)	Consistent	1.16 (1.07,1.27) (Brunekreef et al., 2012b)	Consistent	No evidence of reverse causation bias	Proposed mechanism related to endotoxin exposure, although unclear
2 or more siblings	0.95 (0.90, 0.99)	1.11 (0.88, 1.40)	The estimates are in opposing directions but the individual CI is contained within the school level CI	[d]Categorical No siblings 1.00 (ref) One sibling 1.09 (1.03, 1.15) 2 siblings 1.01 (0.95, 1.08) 3+ siblings 1.04 (0.97, 1.12) (Strachan et al., 2015)	Hard to compare due to different models	If there is an effect, it appears small. There is no dose response relationship (from previous analysis)	-
Heavy truck traffic (current)	1.11 (1.06, 1.16)	0.81 (0.65, 1.02)	The estimates are in opposing directions with a harmful effect at the individual level	[d]Categorical Never 1.00 (ref) Low 1.07 (0.99, 1.15) Med 1.18 (1.09, 1.28) Heavy 1.36 (1.23, 1.50) (Brunekreef et al., 2009)	Consistent with the individual level estimate	May relate to bias- parents of children with eczema may move if they are concerned about traffic exposure	Unlikely causal

Fast food (current)	0.99 (0.94, 1.04)	0.96 (0.76, 1.22)	Consistent	[d]Categorical Never/Occasional 1.00 (ref) 1-2/wk 1.04 (0.99, 1.09) 3+/wk 1.04 (0.95, 1.14) (Ellwood et al., 2013)	Consistent	No evidence of effect	-
Paternal tobacco (current)	1.04 (0.99, 1.10)	0.83 (0.61, 1.13)	The estimates are in opposing directions but the confidence intervals overlap substantially	1.09 (1.04, 1.13) (Mitchell et al., 2012)	Consistent with individual level effect	Very weak association only	No dose response relationship, unlikely causal
Maternal tobacco (current)	1.06 (0.99, 1.13)	1.61 (1.14, 2.25)	The school level harmful effect is much greater	1.15 (1.09, 1.21) (Mitchell et al., 2012)	Shows a stronger effect than the individual level in the current analysis		No dose response relationship, unlikely causal
Paracetamol (current)	1.45 (1.37, 1.54)	1.55 (1.10, 2.21)	Consistent	[d]Categorical Never/Low 1.00 (ref) Med 1.18 (1.08,1.30) High 1.87 (1.68,2.08) (Beasley et al., 2008)	Consistent, the high level is the equivalent to a positive response in the current analysis	No evidence of reverse causation bias	Depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to mainly Th2 immune response. (Beasley et al., 2008, Peterson et al., 1998)

Open fire cooking (current)	1.12 (0.95, 1.32)	1.84 (0.98, 3.45)	Stronger harmful effect seen at school level	1.10 (0.91-1.33) (Wong et al., 2013)	Consistent with individual level effect from current analysis	Possible avoidance bias as people with children with AE remove open fires, masking the true magnitude of effect	Persistent AE may be associated with impaired skin barrier and more likely to react to aeroallergens and irritants

a - fully adjusted for sex, mothers' education level and all other variables in the table

b - fully adjusted for sex, mothers' education level and school level prevalence of all other variables in the table

c - could be adjusted for a variety of different variables

d - no direct comparison possible, so closest results are shown

Table 4. Associations between eczema symptoms in the last 12 months and risk factors for 13-14 year old age group comparing results from different analyses

Exposure	Current analysis			Previous ISAAC analysis		Assessment of bias	Biological plausibility of effect
	Individual	School level[b]	Comparison	Individual level[c]	Comparison with current analysis		
2 or more siblings	1.08 (1.03,1.12)	1.26 (0.97, 1.65)	The school level shows a stronger harmful effect although the CI includes the full	[d]Categorical No siblings 1.00 (ref) One sibling 0.91 (0.85, 0.98) 2 siblings 0.96 (0.88,	Consistent, although not easy to compare		May represent a chance association. No dose-response relationship in individual studies.
Heavy truck traffic **(current)**	1.31 (1.27, 1.36)	1.40 (1.07, 1.82)	Consistent	[d]Categorical Never 1.00 (ref) Low 1.08 (0.97, 1.19) Med 1.30 (1.17, 1.45) Heavy 1.54 (1.37, 1.73) (Brunekreef et al., 2009)	Consistent	No evidence of reverse causation bias	Previous studies demonstrated dose-response relationship between levels of exposure to traffic and AE symptoms. No clearly established biological mechanism. Inverse school-level association found in 6-7-year-olds contrasts with the positive school-level association shown here for 13-14-year-olds, suggesting caution in drawing firm conclusions regarding causality.

Fast food (current)	1.05 (1.02, 1.10)	2.11 (1.66, 2.70)	The school level shows a stronger harmful effect	[d]Categorical Never/Occasional 1.00 (ref) 1-2/wk 1.04 (0.99, 1.10) 3+/wk 1.20 (1.11, 1.28) (Ellwood et al., 2013)	Consistent with individual level effect in current analysis	Possible avoidance bias as people with adolescents with AE avoid fast food, masking the true magnitude of effect	Not fully understood; theories around ingested fatty acids and inflammation.
Paternal tobacco (current)	1.15 (1.10, 1.19)	0.64 (0.44, 0.94)	The estimates are in opposing directions but the confidence intervals overlap substantially; school-level estimates look protective.	1.19 (1.14, 1.25) (Mitchell et al., 2012)	Consistent with individual level effect in current analysis	The finding might support differential reporting of tobacco exposure in those with current AE symptoms or ecologic bias at school level	-
Maternal tobacco (current)	1.11 (1.06, 1.16)	0.79 (0.52, 1.19)	The estimates are in opposing directions but the confidence intervals overlap substantially	1.22 (1.16, 1.28) (Mitchell et al., 2012)	Stronger effect than current individual level analysis	As for paternal tobacco.	-

Paracetamol (current)	1.57 (1.51, 1.63)	2.57 (1.84, 3.59)	The school level harmful effect is much greater	[d]Categorical Never/Low 1.00 (ref) Med 1.31 (1.21, 1.42) High 1.99 (1.82, 2.16) (Beasley et al., 2011)	Consistent with individual level current analysis (High is the same as the positive value in current analysis)	Some evidence of possible avoidance bias masking the true magnitude of the harmful effect	Possible biological mechanisms underlying the observed association between paracetamol use and AE may relate to a depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to a predominantly Th2 immune response (Beasley et al., 2011, Peterson et al., 1998).
Open fire cooking (current)	1.46 (1.33, 1.62)	2.38 (1.52, 3.73)	Stronger harmful effect seen at school level.	1.37 (1.13-1.66) (Wong et al., 2013)	Consistent with individual level effect in current analysis	Possible avoidance bias as people with asthmatic children remove open fires, masking the true magnitude of effect	Persistent AE may be associated with impaired skin barrier and more likely to react to aeroallergens and irritants.

a - fully adjusted for sex, mothers' education level and all other variables in the table

b - fully adjusted for sex, mothers' education level and school level prevalence of all other variables in the table

c - could be adjusted for a variety of different variables

d - no direct comparison possible, so closest results are shown

Figure legends

Fig. 1. Atopic eczema data flowchart, age 6-7 years

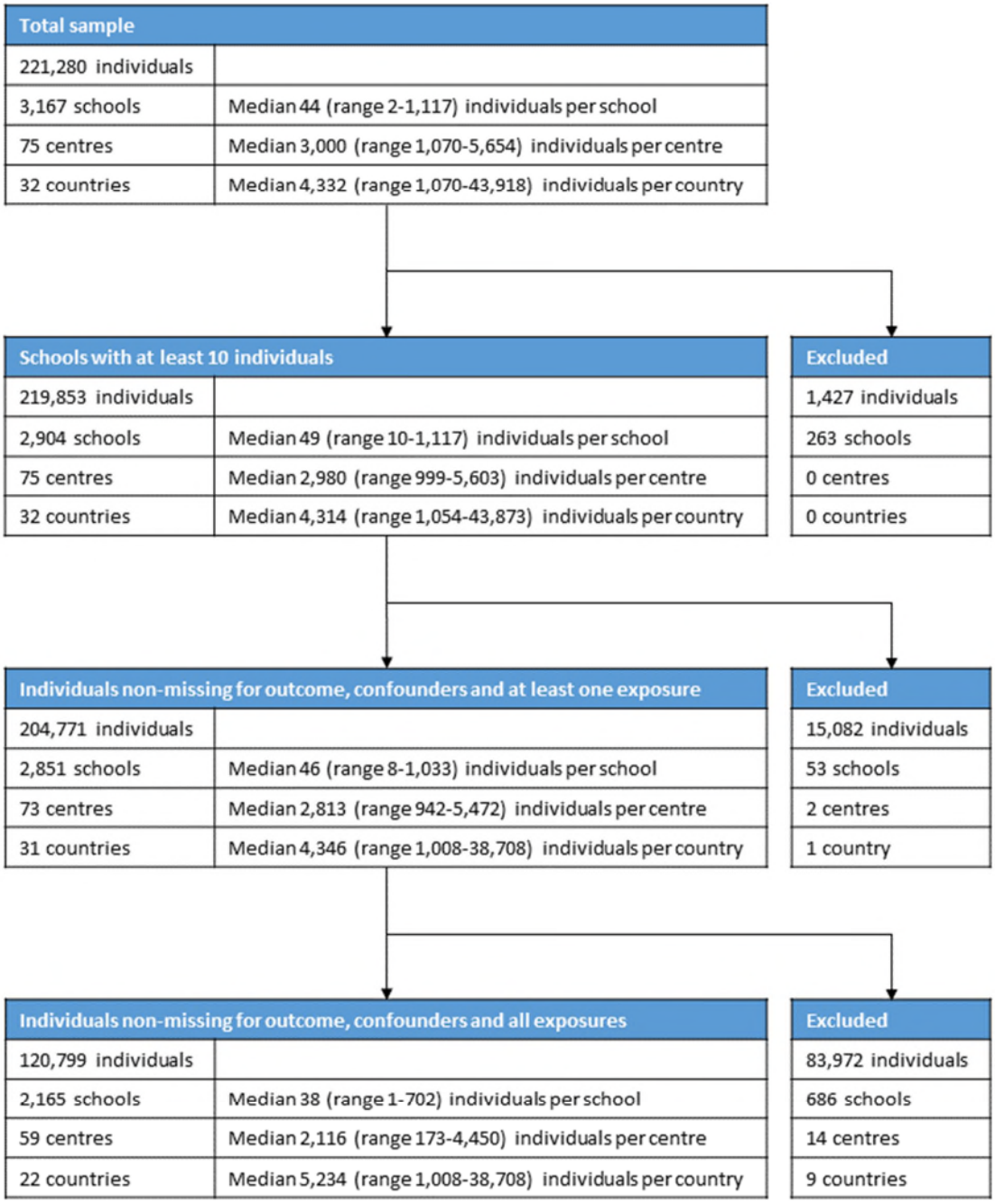
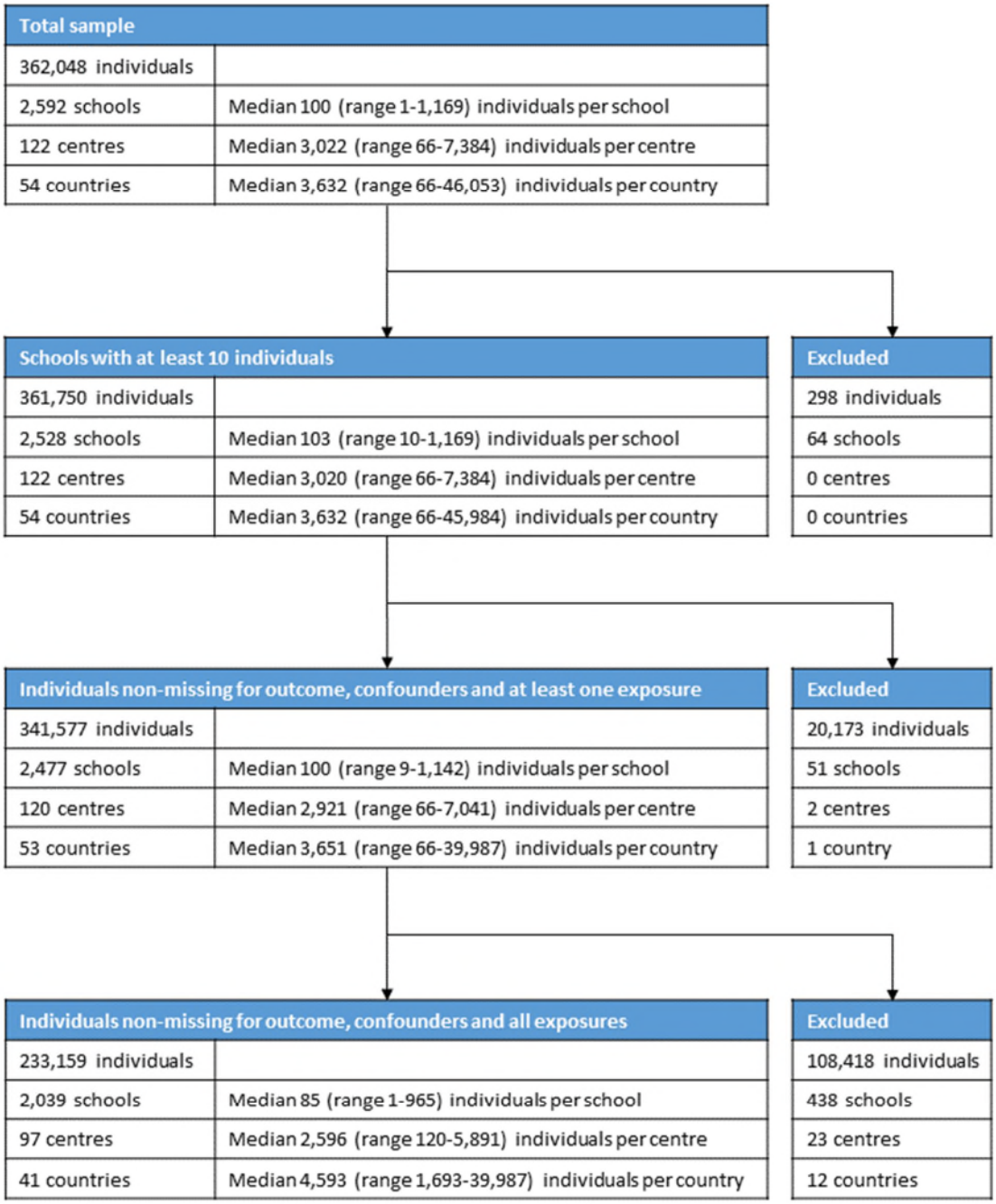


Fig. 2. Atopic eczema data flowchart, age 13-14 years.



Supplementary Material

Supplementary methods

Centre and school eligibility criteria

Only centres that met ISAAC methodology standards were included in the analysis. Excluded centres were those with fewer than 1,000 participants or response rates below 60% for the 6-7 year-old age group or below 70% for the 13-14 year-olds. Centres were also excluded if they did not return the Centre Report (Ellwood et al., 2005). Schools with fewer than 10 participants for a given age group were excluded from that analysis.

Environmental risk factors

Analyses in this paper included only the key environmental variables previously each singly associated with AE in ISAAC at an individual-level. For the 6-7 year olds, risk factors were paracetamol use in the first year of life and in the past 12 months (Beasley et al., 2008), antibiotic use in the first year of life (Foliaki et al., 2009), breast feeding (Bjorksten et al., 2011), cat and dog in the home in the first year of life (Brunekreef et al., 2012a), regular contact with farm animals in the first year of life (Brunekreef et al., 2012b), regular maternal contact with farm animals while pregnant (Brunekreef et al., 2012b), heavy truck traffic (Brunekreef et al., 2009), fast food consumption (Ellwood et al., 2013), parental smoking (Mitchell et al., 2012), cooking on an open fire (Wong et al., 2013), birthweight (Mitchell et al., 2014) and number of siblings (Strachan et al., 2015). For the 13-14 year olds, risk factors were heavy truck traffic (Brunekreef et al., 2009), fast food consumption (Ellwood et al., 2013), parental smoking (Mitchell et al., 2012), paracetamol use in the past 12 months (Beasley et al., 2011), open fire cooking (Wong et al., 2013), and number of siblings (Strachan et al., 2015).

Most of these items had simple “yes/no” answers. The exceptions have been dichotomised: paracetamol use in the last 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), low birthweight (less than 2.5 kg vs. at least 2.5 kg), and number of siblings (2 or more vs. 1 or fewer). Full definitions of the environmental risk factors are in Table S2 of the Supplementary Material.

Derivation of affluence

Gross National Income (GNI) as of 2002 (obtained from the World Bank website (The World Bank, 2016a) where available and filled in by the Central Intelligence Agency (CIA) World Factbook (Central Intelligence Agency, 2002)) and a classification of affluent countries (GNI over US$9,205) and non-affluent countries (GNI US$9,205 or lower) taken from the 2001 World Bank definition of high-income countries versus low- to middle-income countries (The World Bank, 2016b).

Table S1: Summary statistics in subjects with data for atopic eczema symptoms, sex, level of maternal education and the one exposure of interest (the "maximum sample").

Age group	Variable	Individual-level		School-level		
		n	Prevalence	n	Median prevalence	Prevalence IQR
6-7 years	Atopic eczema in the last 12 months	204,771	0.074	2,851	0.067	(0.029, 0.116)
	Farm animals (in utero)	181,600	0.100	2,630	0.078	(0.034, 0.156)
	Low birthweight	169,993	0.085	2,549	0.063	(0.032, 0.106)
	Paracetamol (1st year)	182,134	0.652	2,583	0.700	(0.563, 0.826)
	Antibiotics (1st year)	180,799	0.540	2,663	0.559	(0.462, 0.646)
	Breastfed ever	192,559	0.800	2,701	0.846	(0.736, 0.929)
	Cat (1st year)	189,922	0.120	2,701	0.105	(0.048, 0.200)
	Dog (1st year)	174,772	0.206	2,469	0.222	(0.123, 0.328)
	Farm animals (1st year)	181,744	0.116	2,634	0.098	(0.046, 0.178)
	2 or more siblings	203,603	0.381	2,851	0.375	(0.222, 0.544)
	Heavy Truck traffic (current)	184,503	0.386	2,729	0.382	(0.278, 0.491)
	Fast food (current)	181,864	0.411	2,798	0.333	(0.185, 0.511)
	Paternal tobacco (current)	196,353	0.313	2,748	0.333	(0.193, 0.465)
	Maternal tobacco (current)	199,522	0.141	2,781	0.140	(0.030, 0.301)
	Paracetamol (current)	191,900	0.198	2,734	0.167	(0.079, 0.313)
	Open fire cooking (current)	185,718	0.030	2,724	0.000	(0.000, 0.022)
13-14 years	Atopic eczema in the last 12 months	341,577	0.068	2,477	0.055	(0.027, 0.102)
	2 or more siblings	334,708	0.552	2,402	0.621	(0.389, 0.810)
	Heavy Truck traffic (current)	309,621	0.396	2,348	0.394	(0.303, 0.510)
	Fast food (current)	313,066	0.552	2,388	0.552	(0.407, 0.695)
	Paternal tobacco (current)	301,502	0.376	2,259	0.367	(0.239, 0.482)
	Maternal tobacco (current)	329,659	0.181	2,433	0.183	(0.040, 0.333)
	Paracetamol (current)	314,005	0.288	2,404	0.310	(0.195, 0.435)
	Open fire cooking (current)	303,363	0.073	2,321	0.011	(0.000, 0.047)

Table S2: Risk Factor definitions

Risk factors for ages 6-7	**Question (asked to parent)**	**Positive Response**
Farm animals (in utero)	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
Low birthweight	What was the weight of your child when he / she was born?	Less than 2.5kg
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
Breastfed ever	Was your child breastfed?	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
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
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
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 a 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
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 a 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 S3. Minimally adjusted[A] effects of individual- and school-level exposures on atopic eczema symptoms in the last 12 months in subjects with data for atopic eczema symptoms, sex, level of maternal education and the one exposure of interest (the "maximum sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.

Age group	Exposure	Individual-level exposure		School-level exposure	
		n	OR (95% CI)	n	OR (95% CI)
6-7 years	Farm animals (in utero)	181,600	1.37 (1.29, 1.45)	181,600	1.85 (1.39, 2.45)
	Low birthweight	169,993	0.93 (0.86, 1.00)	169,993	1.65 (1.07, 2.55)
	Paracetamol (1st year)	182,134	1.55 (1.48, 1.62)	182,134	1.12 (0.87, 1.44)
	Antibiotics (1st year)	180,799	1.60 (1.53, 1.66)	180,799	1.29 (1.00, 1.66)
	Breastfed ever	192,559	1.09 (1.04, 1.14)	192,559	0.94 (0.69, 1.26)
	Cat (1st year)	189,922	1.27 (1.21, 1.34)	189,922	1.79 (1.33, 2.41)
	Dog (1st year)	174,772	1.16 (1.11, 1.21)	174,772	1.48 (1.14, 1.92)
	Farm animals (1st year)	181,744	1.41 (1.34, 1.49)	181,744	2.06 (1.56, 2.72)
	2 or more siblings	203,603	0.98 (0.94, 1.01)	203,603	1.44 (1.20, 1.73)
	Heavy Truck traffic (current)	184,503	1.19 (1.14, 1.23)	184,503	1.15 (0.94, 1.39)
	Fast food (current)	181,864	1.03 (0.99, 1.07)	181,864	0.84 (0.69, 1.02)
	Paternal tobacco (current)	196,353	1.11 (1.07, 1.16)	196,353	1.27 (1.01, 1.60)
	Maternal tobacco (current)	199,522	1.17 (1.11, 1.22)	199,522	1.61 (1.24, 2.09)
	Paracetamol (current)	191,900	1.60 (1.53, 1.67)	191,900	1.69 (1.28, 2.23)
	Open fire cooking (current)	185,718	1.14 (1.02, 1.29)	185,718	2.98 (1.83, 4.85)
Age group	Exposure	Individual-level exposure		School-level exposure	
		n	OR (95% CI)	n	OR (95% CI)
13-14 years	2 or more siblings	334,708	1.06 (1.03, 1.10)	334,708	1.25 (0.99, 1.57)
	Heavy Truck traffic (current)	309,621	1.31 (1.27, 1.35)	309,621	1.53 (1.20, 1.96)
	Fast food (current)	313,066	1.09 (1.06, 1.13)	313,066	1.85 (1.48, 2.32)
	Paternal tobacco (current)	301,502	1.22 (1.18, 1.26)	301,502	0.72 (0.54, 0.96)
	Maternal tobacco (current)	329,659	1.23 (1.19, 1.28)	329,659	0.91 (0.66, 1.24)
	Paracetamol (current)	314,005	1.57 (1.52, 1.62)	314,005	2.14 (1.59, 2.88)
	Open fire cooking (current)	303,363	1.43 (1.34, 1.53)	303,363	1.50 (1.09, 2.06)

[A]Adjusted for sex and mothers level of education.

Table S4. Fully adjusted[A] effects of individual-level exposures on atopic eczema symptoms in the last 12 months in subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample"), stratified by country-level affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Age group	Exposure	Affluent Countries (n = 43,374)		Non-Affluent countries (n = 77,425)		Effect modification p-value
		Number exposed (%)	OR (95% CI)	Number exposed (%)	OR (95% CI)	
6-7 years	Farm animals (in utero)	2,970 (6.8)	1.00 (0.84, 1.20)	6,365 (8.2)	1.19 (1.06, 1.35)	<0.001
	Low birthweight	2,508 (5.8)	0.92 (0.80, 1.06)	6,763 (8.7)	0.85 (0.76, 0.96)	0.51
	Paracetamol (1st year)	27,222 (62.8)	1.29 (1.17, 1.41)	52,751 (68.1)	1.30 (1.21, 1.40)	0.93
	Antibiotics (1st year)	22,736 (52.4)	1.44 (1.34, 1.55)	44,504 (57.5)	1.37 (1.28, 1.47)	0.33
	Breastfed ever	29,658 (68.4)	1.16 (1.07, 1.25)	67,532 (87.2)	1.05 (0.97, 1.15)	0.11
	Cat (1st year)	6,717 (15.5)	1.01 (0.92, 1.10)	6,508 (8.4)	1.21 (1.09, 1.33)	<0.001
	Dog (1st year)	8,102 (18.7)	0.98 (0.90, 1.06)	15,790 (20.4)	1.09 (1.02, 1.17)	<0.001
	Farm animals (1st year)	3,688 (8.5)	0.96 (0.81, 1.13)	7,662 (9.9)	1.29 (1.15, 1.44)	<0.001
	2 or more siblings	12,887 (29.7)	0.95 (0.89, 1.03)	29,066 (37.5)	0.93 (0.87, 1.00)	0.95
	Heavy Truck traffic	14,353 (33.1)	1.07 (1.00, 1.15)	31,515 (40.7)	1.14 (1.07, 1.21)	0.14
	Fast food (current)	13,496 (31.1)	1.05 (0.97, 1.13)	34,343 (44.4)	0.96 (0.89, 1.02)	0.10
	Paternal tobacco (current)	16,991 (39.2)	1.05 (0.98, 1.14)	21,468 (27.7)	1.04 (0.97, 1.11)	0.40
	Maternal tobacco	12,058 (27.8)	1.00 (0.92, 1.08)	7,620 (9.8)	1.15 (1.05, 1.26)	0.008
	Paracetamol (current)	5,011 (11.6)	1.64 (1.49, 1.79)	16,724 (21.6)	1.35 (1.25, 1.45)	0.003
	Open fire cooking	255 (0.6)	1.09 (0.73, 1.63)	2,000 (2.6)	1.10 (0.92, 1.33)	0.60
Age group	Exposure	Affluent Countries (n=48,626)		Non-Affluent Countries (n=184,533)		Effect modification p-value
		Number exposed (%)	OR (95% CI)	Number exposed (%)	OR (95% CI)	
13-14 years	2 or more siblings	18,086 (37.2)	1.06 (0.97, 1.16)	108,122 (58.6)	1.08 (1.03, 1.13)	0.51
	Heavy Truck traffic	17,725 (36.5)	1.32 (1.21, 1.44)	74,568 (40.4)	1.31 (1.26, 1.37)	0.81
	Fast food (current)	24,780 (51.0)	1.06 (0.97, 1.15)	100,139 (54.3)	1.06 (1.01, 1.10)	0.79
	Paternal tobacco (current)	19,486 (40.1)	1.05 (0.96, 1.14)	70,043 (38.0)	1.17 (1.12, 1.23)	0.01
	Maternal tobacco	14,713 (30.3)	1.09 (0.99, 1.20)	27,899 (15.1)	1.12 (1.06, 1.18)	0.31
	Paracetamol (current)	13,211 (27.2)	1.75 (1.60, 1.92)	49,682 (26.9)	1.53 (1.47, 1.60)	0.007
	Open fire cooking	513 (1.1)	1.55 (1.10, 2.18)	11,565 (6.3)	1.44 (1.30, 1.60)	0.73

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

Table S5: Fully adjusted[A] effects of school-level exposures on prevalence on atopic eczema symptoms in the last 12 month in subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample"), stratified by country-level affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.

Age group	Exposure	Affluent countries (n = 43,374)		Non-affluent countries (n = 77,425)		Effect modification p-value
		Median prevalence	OR (95% CI)	Median prevalence	OR (95% CI)	
6-7 years	Farm animals (in utero)	0.06	1.51 (0.56, 4.03)	0.07	0.77 (0.30, 1.97)	0.13
	Low birthweight	0.05	1.16 (0.49, 2.73)	0.06	1.87 (0.94, 3.70)	0.19
	Paracetamol (1st year)	0.76	1.29 (0.82, 2.05)	0.68	0.88 (0.58, 1.34)	0.28
	Antibiotics (1st year)	0.57	1.39 (0.91, 2.12)	0.58	1.23 (0.79, 1.90)	0.41
	Breastfed ever	0.74	1.15 (0.77, 1.71)	0.89	0.83 (0.45, 1.54)	0.35
	Cat (1st year)	0.10	1.02 (0.64, 1.64)	0.08	1.45 (0.68, 3.09)	0.03
	Dog (1st year)	0.19	0.79 (0.51, 1.24)	0.21	1.18 (0.72, 1.92)	0.03
	Farm animals (1st year)	0.08	0.57 (0.22, 1.47)	0.09	1.86 (0.81, 4.31)	0.02
	2 or more siblings	0.28	1.01 (0.72, 1.40)	0.36	1.08 (0.77, 1.51)	0.44
	Heavy Truck traffic (current)	0.33	0.83 (0.60, 1.14)	0.40	0.83 (0.60, 1.16)	0.77
	Fast food (current)	0.27	0.79 (0.54, 1.17)	0.36	1.11 (0.81, 1.52)	0.34
	Paternal tobacco (current)	0.42	1.02 (0.67, 1.55)	0.29	0.61 (0.38, 0.99)	0.57
	Maternal tobacco (current)	0.30	1.43 (0.96, 2.14)	0.08	1.88 (1.01, 3.51)	0.54
	Paracetamol (current)	0.12	2.05 (1.23, 3.42)	0.17	1.35 (0.83, 2.22)	0.38
	Open fire cooking (current)	0.00	2.75 (0.40, 18.79)	0.00	1.62 (0.80, 3.27)	0.97
Age group	Exposure	Affluent countries (n = 48,626)		Non-affluent countries (n = 184,533)		Effect modification p-value
		Median prevalence	OR (95% CI)	Median prevalence	OR (95% CI)	
13-14 years	2 or more siblings	0.35	1.26 (0.76, 2.10)	0.68	1.33 (0.97, 1.82)	0.16
	Heavy Truck traffic (current)	0.37	0.99 (0.53, 1.84)	0.40	1.47 (1.10, 1.97)	0.12
	Fast food (current)	0.50	1.40 (0.80, 2.43)	0.55	2.42 (1.84, 3.20)	0.03
	Paternal tobacco (current)	0.43	0.45 (0.21, 0.95)	0.34	0.73 (0.47, 1.12)	0.16
	Maternal tobacco (current)	0.35	1.46 (0.68, 3.12)	0.13	0.64 (0.39, 1.04)	0.48
	Paracetamol (current)	0.30	2.38 (1.26, 4.51)	0.29	2.62 (1.79, 3.85)	0.58
	Open fire cooking (current)	0.00	1.08 (0.04, 26.81)	0.01	2.26 (1.40, 3.66)	0.45

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