European Journal of Epidemiology (2019) 34:509–520
https://doi.org/10.1007/s10654-018-0463-z

RESPIRATORY EPIDEMIOLOGY

Can environment or allergy explain international variation in prevalence of wheeze in childhood?

Gudrun Weinmayr[1] · Andrea Jaensch[1] · Ann-Kathrin Ruelius[1] · Francesco Forastiere[2] · David P. Strachan[3] · the ISAAC Phase Two Study Group

Received: 28 March 2018 / Accepted: 2 November 2018 / Published online: 11 November 2018

Abstract

Asthma prevalence in children varies substantially around the world, but the contribution of known risk factors to this international variation is uncertain. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two studied 8–12 year old children in 30 centres worldwide with parent-completed symptom and risk factor questionnaires and aeroallergen skin prick testing. We used multilevel logistic regression modelling to investigate the effect of adjustment for individual and ecological risk factors on the between-centre variation in prevalence of recent wheeze. Adjustment for single individual-level risk factors changed the centre-level variation from a reduction of up to 8.4% (and 8.5% for atopy) to an increase of up to 6.8%. Modelling the 11 most influential environmental factors among all children simultaneously, the centre-level variation changed little overall (2.4% increase). Modelling only factors that decreased the variance, the 6 most influential factors (synthetic and feather quilt, mother's smoking, heating stoves, dampness and foam pillows) in combination resulted in a 21% reduction in variance. Ecological (centre-level) risk factors generally explained higher proportions of the variation than did individual risk factors. Single environmental factors and aeroallergen sensitisation measured at the individual (child) level did not explain much of the between-centre variation in wheeze prevalence.

Keywords Asthma · Child · Hypersensitivity · Environmental risk factors · International variation

Introduction

Asthma poses an important health burden worldwide, but its aetiology is still not fully understood, particularly in low- and middle-income countries. For instance, allergic mechanisms which have been widely studied in high-income countries appear to be less important in less affluent settings [1]. There are substantial differences in childhood asthma prevalence worldwide [2] as described in Phases One and Three of the International Study of Asthma and Allergy in Childhood (ISAAC), which are also apparent in ISAAC Phase Two where allergic sensitization was assessed by aeroallergen skin prick testing [3]. It is not known how much of this international variation in wheeze prevalence is explained by differences in allergic sensitization or other individual-level risk factors. If the currently well-established risk factors fail to explain a substantial part of the international variation this would indicate that important risk factors are still undiscovered. In addition to these child-level risk factors (e.g. the child is vaccinated against measles), contextual factors at the population level (e.g. the proportion of the population that is vaccinated against measles), may also be relevant in determining prevalence. Additionally, ecological (population-level) analyses may inform about risk factors that vary little within a given population but vary markedly in prevalence between different populations, e.g. factors

All investigators in the Phase Two Study Group are listed in the "Appendix".

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10654-018-0463-z) contains supplementary material, which is available to authorized users.

✉ Gudrun Weinmayr
Gudrun.Weinmayr@uni-ulm.de

[1] Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstraße 22, 89081 Ulm, Germany

[2] Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

[3] Population Health Research Institute, St George's, University of London, London, UK

related to a "Western" life style. Early attempts to exploit prevalence differences to understand the role of individual level risk factors in allergic disease were undertaken in Germany and China, by comparing one population with a highly Westernized lifestyle (e.g. West Germany, Hong Kong) to a population of the same ethnic background that was much less Westernized (e.g. East-Germany, mainland China) [4, 5]. The Chinese study concluded that lifestyle and environmental risk factors that varied between Hong Kong and mainland China could "explain away" the prevalence difference between the two populations. However, such a comparison of only two centres is inherently limited in terms of generalizability.

In this paper, we extended this approach to thirty diverse study centres, including the German and Chinese centres previously studied, to quantify the extent to which known and suspected individual and contextual (ecological) risk factors may explain the observed large international variation in the prevalence of wheeze in children using data from ISAAC Phase Two.

Methods

Study population and fieldwork

The methods of ISAAC Phase Two have been described in detail elsewhere [3]. Briefly, random samples of at least 10 schools from defined geographical areas were chosen and children ($n \geq 1000$ per centre) attending classes with a majority of 9–11-year-olds were invited to participate. Standardized parental questionnaires were used. In a few centres, skin prick tests and risk factor questionnaires were carried out in stratified subsamples targeting 100 children with and without wheeze in the past year, respectively (details see Online Resource).

Thirty centres in twenty-two countries participated in the questionnaire survey and 29 centres from 21 countries performed the standardized skin prick test.

Outcome

The main symptom of asthma used in this analysis was "wheeze in the past year". Analyses were also carried out separately for wheeze among atopic and among non-atopic children. Children were defined as atopic if the skin prick test to any of the six aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, *Alternaria tenuis*, mixed tree pollen and mixed grass pollen) or any other locally tested allergen was positive [1]. The standardized protocol can be found online [6].

Exposures

The detailed questionnaire for environmental risk factors is available online [6] and covers environmental and life style risk factors in the domains of early day exposures, diseases and immunizations, the child's home (indoor air, animals and other living conditions), exercise and food. The questionnaire enquired "Have you made any changes in your home because your child had asthma or allergic problems?", with subsequent specifications which were each answered separately: removed pets, stopped or reduced smoking, changed pillows, changed bedding, changed floor covering. This helps us to address concerns about reverse causality in this cross-sectional study. We compared child-level associations (within-centre) before and after exclusion of those reporting changes to the relevant risk factor and present these results in supplementary table E2 on the Online Resource.

Furthermore, we retrieved potentially relevant ecological variables from publicly available data sources (for detailed description see Online Resource). Because many potentially relevant factors are not available from such sources we additionally derived, by aggregation, centre-level covariates from the questionnaires: from the individual data on risk factors, we constructed ecological variables giving the prevalence of the individual risk factor in the centre—for details see Online Resource. We did this for all available risk factors acknowledging that some of the resulting variables may be indicators for other centre-level risk factors.

Statistical approach

In this analysis, we were interested in the variation of wheeze prevalence in this international multicentre study that is due to true underlying variation between centres and not to the play of chance (sampling error). We also sought to estimate how much of the non-sampling variation could be explained by between-centre differences in the prevalence of individual or ecological factors associated with wheeze. Within the framework of a multilevel logistic regression analysis with individuals as the first level and centres as the second level, the "true" wheeze prevalence for each centre is reflected (on a logodds scale) by the random intercept for that centre, and the between-centre variation can be summarised by the variance of the distribution of the random intercepts (tau^2).

When introducing explanatory variables the variance tau^2 changes: introducing ecological (centre-level) variables will always lead to a reduction because only the between-centre variance is affected. For individual-level variables, where

both the individual-level and centre-level variation are affected, a change in tau^2 can occur in either direction [7].

In order to reduce the between-centre variation, an individual-level variable must be either a risk factor (increasing child's risk of wheezing) and more common in centres with higher prevalence of disease, or a protective factor at the individual level and inversely correlated with the prevalence of disease at the centre level. There are also cases where a risk factor may be inversely correlated with wheeze prevalence at the centre level, or a protective factor may be more common in centres with higher prevalence of disease. In those instances, adjustment for the child-level associations in the multi-level model will increase (not decrease) the between-centre variation (tau^2). Thus, adjustment for individual-level variables can either decrease ("explain away") or increase ("accentuate") between-centre differences in disease prevalence.

In contrast to continuous outcomes and linear models, the variance at individual level in the logistic model is determined by the binomial distribution of the dichotomous outcome and therefore, models that differ in explanatory variables cannot be compared directly regarding their coefficients and their tau^2. To allow a direct comparison, we used a scaling method [8], as described in detail elsewhere [7]. Hence we compared the rescaled tau^2 of risk factor models to the rescaled tau^2 of the null model without any explanatory factors.

For some risk factors in some centres, the case–control design gives artificially high intercepts because the stratified subsample is enriched for wheezy children. This was corrected in our multi-level model by using the appropriate sampling weights for wheezy and non-wheezy children in these stratified subsamples [9] (for details see Online Resource).

Construction of models with explanatory variables and determination of the change in tau^2

A detailed description can be found in the Online Resource. In brief, we first tested all individual level and ecological variables in single risk factor models i.e. only one explanatory variable was introduced. The tau^2 of these models was compared to the tau^2 of the null model: the relative change (in percent) in tau^2 with regard to the tau^2 of the null model was calculated.

The individual risk factors to be introduced in multivariate models were chosen from the risk factors that engendered the greatest change in tau^2. From previous work with the ISAAC data we know that so far adjustment with potential confounders had very little influence on effect estimates in this multicentre international context (see e.g. [10, 11]).

To avoid important losses in the number of children analysed in the multivariate models, we adopted a simple approach to substitute the missing values with mean values (for details see the Online Resource). We also performed analyses stratified by atopy because the relevant environmental risk factors may differ between atopic and non-atopic children reflecting atopic and non-atopic wheeze [1, 12].

All analyses were carried out using Stata releases 10 and 14 using gllamm (http://www.gllamm.org). The rescaling of coefficients and tau^2 was carried out according to a do-file developed by the authors and published elsewhere [7].

Results

Up to 53,748 children (depending on availability of risk factor information) from 30 centres in 22 countries were included. The prevalence of wheeze in the past year ("recent wheeze") across the 30 centres ranged from 0.8% in Pichincha Province, Ecuador to 25.6% in Uruguaiana, Brazil [1]. Only 2% of the corresponding between centre variation in prevalence could be attributed to binomial sampling error (heterogeneity $I^2 = 98\%$). When the analysis was stratified by skin prick test positivity, the prevalence of recent wheeze among atopic children ranged from 1.1 to 40.5% ($I^2 = 92\%$) and among non-atopic children from 0.5 to 24.1% ($I^2 = 98\%$).

Single risk factor models

Individual level environmental variables

Table 1 shows the 30 variables ascertained at the individual (child) level that lead to the greatest changes in tau^2 when included, each in turn, in the two-level model. The maximum decrease of tau^2 that was related to adjustment for a single individual-level variable was 8.4% for use of a synthetic quilt at present (Table 1, left side). This risk factor had a wide range of prevalence among centres from 1.9 to 87.9%, and was associated with recent wheeze within centres, with an individual-level odds ratio (OR) of 1.33 (95% confidence interval (CI) 1.09–1.61).

Adjustment for 14 other factors (singly) reduced the scaled tau^2 by more than 2% each. These pertained to bedding, smoking habits of the mother, heating of the home and dampness/mould in the living area.

Introducing explanatory individual-level factors into the multi-level model sometimes increased the between-centre variation. The variable resulting in the strongest increase in tau^2 (by 6.8%) was having carpets or rugs in the child's bedroom. This factor had a within-centre OR of 0.78 (95% CI 0.65–0.94) and ranged in prevalence among centres from 6.2 to 98%. Adjustment for worm infection, whooping cough infection, tuberculosis infection, no pillow use and cooking with wood/coal at present, each resulted in an increase of more than 2%.

Table 1 Wheeze prevalence—change in the between-centre variance tau^2 by individual level variables and centre level variables

Risk factor	Prevalence range	Individual level variables (30 centres; 45,297–51,081 children[a])		Centre level variables[b] (30 centres; 53,748 children[c])		Centre-level correlation between wheeze prevalence and risk factor prevalence
		Relative change in tau^2 (%)	OR (LCL–UCL)	Relative change in tau^2 (%)	OR per 10% increase in risk factor prevalence (LCL–UCL)	
Bedding: synthetic quilt (present)	1.9–87.9	−8.4	1.33 (1.09–1.61)	−23.6	1.15 (1.04–1.26)	0.5661
Floor covering: fitted or loose carpets (present)	6.2–98.1	6.8	0.78 (0.65–0.94)	−6.6	1.05 (0.98–1.13)	0.2553
Bedding: synthetic quilt (fy)	2.2–75.2	−6.7	1.28 (1.08–1.53)	−21.8	1.15 (1.04–1.28)	0.5546
Bedding: feather quilt (present)	1.2–61.7	−6.7	0.56 (0.47–0.65)	−8.2	0.88 (0.76–1.04)	−0.2701
Mother smoked during the child's fy of life	0.1–43.8	−5.2	1.23 (1.12–1.36)	−32.7	1.27 (1.11–1.45)	0.6252
Mother smoked during pregnancy	0.2–33.9	−4.8	1.28 (1.13–1.44)	−34.4	1.38 (1.16–1.64)	0.6580
Mother smokes at present	0.1–48.3	−4.1	1.19 (1.07–1.32)	−24.1	1.20 (1.06–1.37)	0.5677
Pillow: feather (present)	0.4–91.9	−3.9	0.60 (0.42–0.85)	−3.3	0.95 (0.86–1.05)	−0.2822
Disease: worm infection	2.4–99.9	3.4	1.31 (1.03–1.65)	−5.0	0.89 (0.78–1.02)	0.1963
Disease: whooping cough	0.6–48.9	3.1	1.62 (1.46–1.80)	−0.8	0.96 (0.81–1.14)	−0.1100
Bedding: feather quilt (fy)	1.2–86.2	−3.0	0.66 (0.58–0.75)	−3.2	0.94 (0.82–1.07)	−0.2075
Heating inside home (fy)	0.8–98.5	−2.9	1.18 (1.04–1.35)	−5.8	1.05 (0.97–1.15)	0.2913
Heating: wood (fy)	0.1–79.6	−2.9	1.22 (0.96–1.55)	−5.7	1.06 (0.96–1.18)	0.4170
Damp or mould (fy)	6.5–36.7	−2.8	1.65 (1.43–1.89)	−5.9	1.24 (0.89–1.73)	0.4396
Heating inside home (present)	0.8–99.9	−2.6	1.11 (1.02–1.21)	−9.0	1.06 (0.99–1.14)	0.4308
Heating: wood (present)	0–77.2	−2.6	1.10 (0.90–1.34)	−24.4	1.16 (1.05–1.29)	0.6639
Vaccination: tuberculosis	16.5–99.7	2.4	1.07 (0.94–1.21)	−21.2	0.90 (0.83–0.97)	−0.3518
Pillow: no pillow (fy)	2.7–56.1	2.3	0.82 (0.69–0.99)	−8.9	1.14 (0.97–1.34)	0.0979
Pillow: feather (fy)	1.3–75.8	−2.2	0.82 (0.71–0.94)	−4.4	0.94 (0.83–1.05)	−0.3412
Cooking: coal/wood (present)	0–99.3	2.1	1.21 (1.11–1.31)	−2.6	0.94 (0.84–1.06)	0.1318
Damp or mould (present)	2.2–47.1	−2.1	1.51 (1.29–1.76)	−2.6	1.09 (0.88–1.35)	0.3975
Pillow: synthetic fibre (fy)	1.1–85.4	2.0	1.23 (1.06–1.42)	−2.4	0.95 (0.85–1.07)	0.0054
Pillow: foam (fy)	0–79.9	−1.7	1.10 (0.97–1.24)	−16.3	1.17 (1.02–1.33)	0.6186
Cooking: coal/wood (fy)	0–99.2	1.7	1.13 (0.93–1.37)	−5.0	0.93 (0.83–1.05)	−0.1531
Cooking: electricity (fy)	0.3–99.2	1.5	0.86 (0.72–1.03)	−0.6	1.01 (0.94–1.09)	0.1574
Heating inside home/cooking: gas, oil, coal, coke, wood (present)	0.8–100	−1.4	1.08 (0.95–1.22)	−6.0	1.06 (0.97–1.15)	0.2283

Table 1 (continued)

Risk factor	Prevalence range	Individual level variables (30 centres; 45,297–51,081 children[a])		Centre level variables[b] (30 centres; 53,748 children[c])		Centre-level correlation between wheeze prevalence and risk factor prevalence
		Relative change in tau^2 (%)	OR (LCL–UCL)	Relative change in tau^2 (%)	OR per 10% increase in risk factor prevalence (LCL–UCL)	
ETS: 10 or more cigarettes	4.5–34.4	− 1.3	1.17 (1.03–1.32)	− 12.8	1.33 (1.00–1.77)	0.5051
Air conditioning: present	1.2–95.4	− 1.3	0.93 (0.85–1.01)	− 9.3	0.91 (0.82–1.02)	− 0.4027
Breastfeeding 6 months or more	13.5–99.4	− 1.2	0.95 (0.86–1.06)	− 4.4	0.94 (0.85–1.03)	0.0776
Cooking: gas (fy)	0.5–98.9	− 1.1	1.10 (0.95–1.29)	− 1.8	1.03 (0.96–1.10)	0.0215

Fy first year of life of the child, *ETS* environmental tobacco smoke, *OR* odds ratio, *LCL* lower confidence interval limit and *UCL* upper confidence interval limit of the 95% confidence interval

This table contains all variables that lead to a change of > 1% in tau^2 when investigated as individual level variables

[a]Differences in the number of children relate to different numbers of missing values for the respective questions: this is because, in the case of stratified subsamples, we did not impute missing values (details see Online Resource)

[b]Each child has the value of the mean exposure for children in its centre, i.e. all children in the same centre have the same contextual exposure

[c]All children with information on wheeze got assigned a value

Changes made because of the asthma or allergy of the child partly influenced the results, depending on the risk factor. Table E2 in the Online Resource shows the results for the centres that have asked these questions which, depending on the risk factor, encompasses more than half up to most of the affluent centres where one would expect changes to occur more often because of the frequency of allergies and the higher education regarding allergic disease. The change is most marked for carpets and rugs where the OR changes to one. For the other factors small to moderate changes were seen which, given the precision of the estimates, are within the limits of chance. In line with this is the fact that these small changes occurred in both directions when excluding children with changes e.g. an increase in the OR for ETS and a decrease for the mother smoking at present.

Analyses of individual level variables stratified by allergic sensitization

Among participants assessed for allergic sensitization (N = 31,301), a positive skin prick test was associated at the individual level with recent wheeze (OR 3.3, 95% CI 2.8–4.0). Adjustment for this measure of atopy, which ranged in prevalence across centres from 1.7 to 45.3%, resulted in a 8.5% decrease of between-centre variation in wheeze prevalence.

When restricting the population to atopic children and non-atopic children, respectively, the pattern (as shown in Table 2 which contains the same variables as Table 1) only partly corresponded to the one for wheeze overall (Table 1). In general, greater changes in tau^2 were seen among atopic children. While adjustment for synthetic bedding resulted in a higher variance change in atopic children compared to non-atopic children, results for feather (quilt and pillow) were inconsistent. Restricting to children where no changes in bedding occurred, yielded an increase in the OR related to synthetic bedding for atopic children and decrease for non-atopic children. However, the changes of the ORs were well within the limits of precision (i.e. the 95% CI). Maternal smoking, especially in pregnancy and at present, seemed to be more influential in non-atopic than in atopic children, in terms of the effect of adjustment on between-centre variation.

Regarding infections, the changes in variance observed in all children when adjusting for worm infection seemed to be mainly driven by non-atopic children. In contrast, adjustment for whooping cough infection and tuberculosis vaccination had a stronger effect among atopic children, with increases of variance of 7.5% and 15.8%, respectively. In both subgroups many OR were imprecisely estimated so the above observations should be interpreted with caution.

The variables inducing the highest changes in tau^2 also differed between atopic and non-atopic children (Table E3 in Online Resource which contains the 30 variables that lead to the highest changes in atopic and non-atopic children, respectively). In atopic children, the numerically most important changes were the increase in variation of 15.8% related to tuberculosis vaccination and the decrease in variation of 15.6% related to synthetic bedding at present. Variables that do not appear in Table 1

Table 2 Wheeze prevalence among atopic and non-atopic children—change in the between-centre variance tau^2 by individual level variables

Risk factor	Wheeze among atopics (29 centres; 6390–7302 children[a])			Wheeze among non-atopics (29 centres; 20,335–23,565 children[a])		
	Prevalence range	Relative change in tau^2 (%)	OR (LCL–UCL)	Prevalence range	Relative change in tau^2 (%)	OR (LCL–UCL)
Bedding: synthetic quilt (present)	4.0–89.8	−15.6	1.54 (1.25–1.90)	3.8–88.3	−4.4	1.29 (1.02–1.62)
Floor covering: fitted or loose carpets (present)	3.9–98.5	8.4	0.68 (0.56–0.83)	6.2–98.2	0.6	0.98 (0.77–1.24)
Bedding: synthetic quilt (fy)	0–85.0	−10.8	1.36 (0.99–1.86)	1.5–74.0	−4.1	1.33 (0.99–1.78)
Bedding: feather quilt (present)	0–59.1	−1.1	0.62 (0.48–0.80)	0.9–61.7	−9.4	0.62 (0.49–0.77)
Mother smoked during the child's fy of life	0–45.7	−3.0	1.20 (1.03–1.39)	0.1–45.4	−7.2	1.50 (1.33–1.69)
Mother smoked during pregnancy	0–32.2	−3.8	1.27 (1.01–1.61)	0.2–35.6	−4.4	1.40 (1.18–1.66)
Mother smokes at present	0–49.5	−1.9	1.16 (1.03–1.32)	0.1–50.4	−4.9	1.37 (1.23–1.52)
Pillow: feather (present)	0–84.8	−2.3	0.66 (0.39–1.13)	0.4–93.8	−2.7	0.81 (0.62–1.07)
Disease: worm infection	2.3–99.4	−0.7	0.96 (0.78–1.18)	2.8–100.0	1.3	1.58 (1.26–1.98)
Disease: whooping cough	0–44.1	7.5	1.86 (1.50–2.31)	0.7–45.6	3.6	1.55 (1.26–1.90)
Bedding: feather quilt (fy)	0–85.9	−2.9	0.63 (0.44–0.90)	1.0–86.7	−3.7	0.68 (0.43–1.08)
Heating inside home (fy)	1.0–98.2	−1.6	1.36 (1.09–1.69)	0.5–96.3	−3.1	1.24 (0.97–1.57)
Heating: wood (fy)	0–80.0	−2.5	1.48 (1.26–1.74)	0.1–79.2	−2.5	1.29 (0.92–1.82)
Damp or mould (fy)	5.6–45.8	−2.7	1.80 (1.50–2.16)	5.6–38.0	−3.1	1.62 (1.29–2.05)
Heating inside home (present)	1.0–96.6	−1.9	1.17 (0.98–1.40)	0.6–98.4	−5.0	1.22 (0.99–1.50)
Heating: wood (present)	0–75.0	−5.9	1.30 (1.04–1.64)	0–78.1	−4.0	1.24 (0.93–1.65)
Vaccination: tuberculosis	14.3–100.0	15.8	1.47 (1.10–1.98)	16.2–99.7	−2.0	0.92 (0.65–1.29)
Pillow: no pillow (fy)	0–57.1	2.0	0.89 (0.78–1.02)	2.6–56.0	1.6	0.77 (0.55–1.07)
Pillow: feather (fy)	1.9–82.1	2.3	1.21 (0.58–2.52)	1.1–77.1	−1.7	0.75 (0.42–1.32)
Cooking: coal/wood (present)	0–100.0	1.2	1.22 (0.86–1.74)	0–99.5	0.8	1.39 (1.18–1.64)
Damp or mould (present)	0–51.9	−2.6	1.61 (1.36–1.90)	1.1–48.1	−2.9	1.41 (1.09–1.83)
Pillow: synthetic fibre (fy)	0.5–97.0	−0.1	1.02 (0.65–1.60)	0.3–85.5	4.6	1.30 (0.85–1.99)
Pillow: foam (fy)	0–77.2	−1.8	1.11 (0.85–1.44)	0–82.2	−2.0	1.13 (0.95–1.35)
Cooking: coal/wood (fy)	0–94.4	0.6	1.13 (0.87–1.45)	0–99.2	2.0	1.25 (0.99–1.57)
Cooking: electricity (fy)	1.0–99.3	3.4	0.74 (0.55–0.99)	0.2–99.2	0.2	0.85 (0.69–1.06)
Heating inside home/cooking: gas, oil, coal, coke, wood (present)	0–100.0	−3.1	1.25 (0.99–1.57)	0.9–100.0	−0.2	1.01 (0.89–1.14)
ETS: 10 or more cigarettes	4.5–38.3	−0.1	1.10 (0.79–1.53)	4.8–34.5	−2.4	1.28 (1.11–1.48)
Air conditioning: present	0–97.0	−0.4	0.83 (0.70–0.98)	0.7–96.9	−2.0	0.91 (0.77–1.06)
Breastfeeding 6 months or more	8.4–100.0	−0.2	0.99 (0.81–1.21)	12.6–99.4	−0.3	0.91 (0.82–1.01)
Cooking: gas (fy)	0–99.0	−0.7	1.39 (1.10–1.76)	0.6–98.9	0.7	0.95 (0.82–1.10)

fy first year of life of the child, *ETS* environmental tobacco smoke, *OR* odds ratio, *LCL* lower confidence interval limit and *UCL* upper confidence interval limit of the 95% confidence interval

This table contains the same variables as Table 1 listing the variables that resulted in the strongest changes of tau^2 in the whole population (as opposed to non-atopic or atopic children only, which is shown in Table E2 in the Online Resource)

[a]Differences in the number of children relate to different numbers of missing values for the respective questions

but were of importance among atopic children are the number of all siblings (OR 1.08, 95% CI 1.00–1.16; 7.8% increase in tau^2), the number of older siblings (OR 1.08, 95% CI 1.01–1.15; 4.6% increase in tau^2) and measles infection (OR 1.40, 95% CI 1.18–1.65; 4.4% increase in tau^2) (Table E3 in Online Resource). Among non-atopic children most of the variables with the strongest changes in tau^2 related to indoor air quality (smoking, heating

and dampness), but also included bedding and whooping cough.

Overall, adjustment for the most influential risk factors tended to lead predominantly to a decrease in variance of prevalence among non-atopic children; in atopic children, however, adjustment for the most influential risk factors more often resulted in an increase in variance.

Centre/country level variables

Ecological variables introduced into the model generally resulted in markedly higher decreases in tau^2 than those seen for individual level variables (Table 1 and Online Resource Tables E4 and E5). The highest decrease of almost 50% was caused by the centre-level prevalence of contact with a dog in the first year of life (Online Resource Table E4). Of the factors in Table 1, the highest decrease was related to centre-level prevalences of maternal smoking, heating with wood, use of synthetic quilt and tuberculosis vaccination. Ecological factors that appeared to influence notably the wheeze prevalence variation, but which were not strongly associated with wheeze at the individual level, were contact to animals, bedroom sharing and cooked green vegetables (Online Resource Table E4). In comparison with individual level variables, the effect estimates for the centre-level average exposures were imprecise due to the limited number of centres (contrasting with the large number of children for estimation of within-centre associations with individual risk factors). Given this limitation, which also applies to the variables from open access data sources, we chose to put our emphasis on an in depth analysis of the individual-level variables and to not pursue the analysis of the ecological variables with a multivariate model.

Among the ecological variables obtained from open access data sources, the strongest reduction in variation of wheeze prevalence was linked to the country-level variables: the proportion of the population living in urban areas (32% reduction) and other indicators of affluence such as migration, and annual urban population growth (Table E4 in Online Resource). The most important centre-level variables were related to temperature variability (inverse association with wheeze) and coastal location (positive association with wheeze).

Table 3 Wheeze prevalence—change in the between-centre variance tau^2 by individual level variables in multivariate models

	All children (N centres = 30, N children = 50,852[a])	Atopic children (N centres = 29, N children = 7285[a])	Non-atopic children (N centres = 29, N children = 23,418[a])
	Relative change in tau^2 (%)	Relative change in tau^2 (%)	Relative change in tau^2 (%)
Factors that result in increase or decrease in tau^2			
Bedding: synthetic quilt at present	−8.4	−16.4	−4.3
Add floor covering: fitted or loose carpet at present	−1.0	−5.2	−6.3
Add bedding: feather quilt at present	−3.7	−3.3	−14.1
Add mother smoked during first year of life	−8.2	−5.0	−20.0
Add worm infection	−4.4	−6.5	−19.0
Add whooping cough	−3.3	−4.7	−16.9
Add heating inside home fy	−5.7	−4.9	−19.7
Add damp or mould fy	−7.9	−5.7	−22.8
Add vaccination: tuberculosis	−3.2	4.1	−20.0
Add pillow: no pillow fy	−0.9	5.6	−18.2
Add cooking: coal/wood at present	2.3	7.3	−15.3
Add pillow: foam fy	2.2	6.7	−15.7
Add cooking: electricity fy	2.4	11.6	−15.9
Only factors that result in a decrease in tau^2 in all children			
Bedding: synthetic quilt at present	−8.4	−16.4	−4.3
Add bedding: feather quilt at present	−10.5	−13.4	−12.0
Add mother smoked during first year of life	−15.0	−15.1	−17.6
Add heating inside home fy	−17.2	−15.0	−21.3
Add damp or mould fy	−19.0	−15.2	−24.9
Add pillow: foam fy	−20.5	−16.8	−26.8

fy first year of life of the child; for choice of variables for multivariate model see Methods section in the Online Resource

[a]In the stratified subsamples only children included with risk factor information were included resulting in 50,852 children (in contrast to the 53,748 children who had information on wheeze)

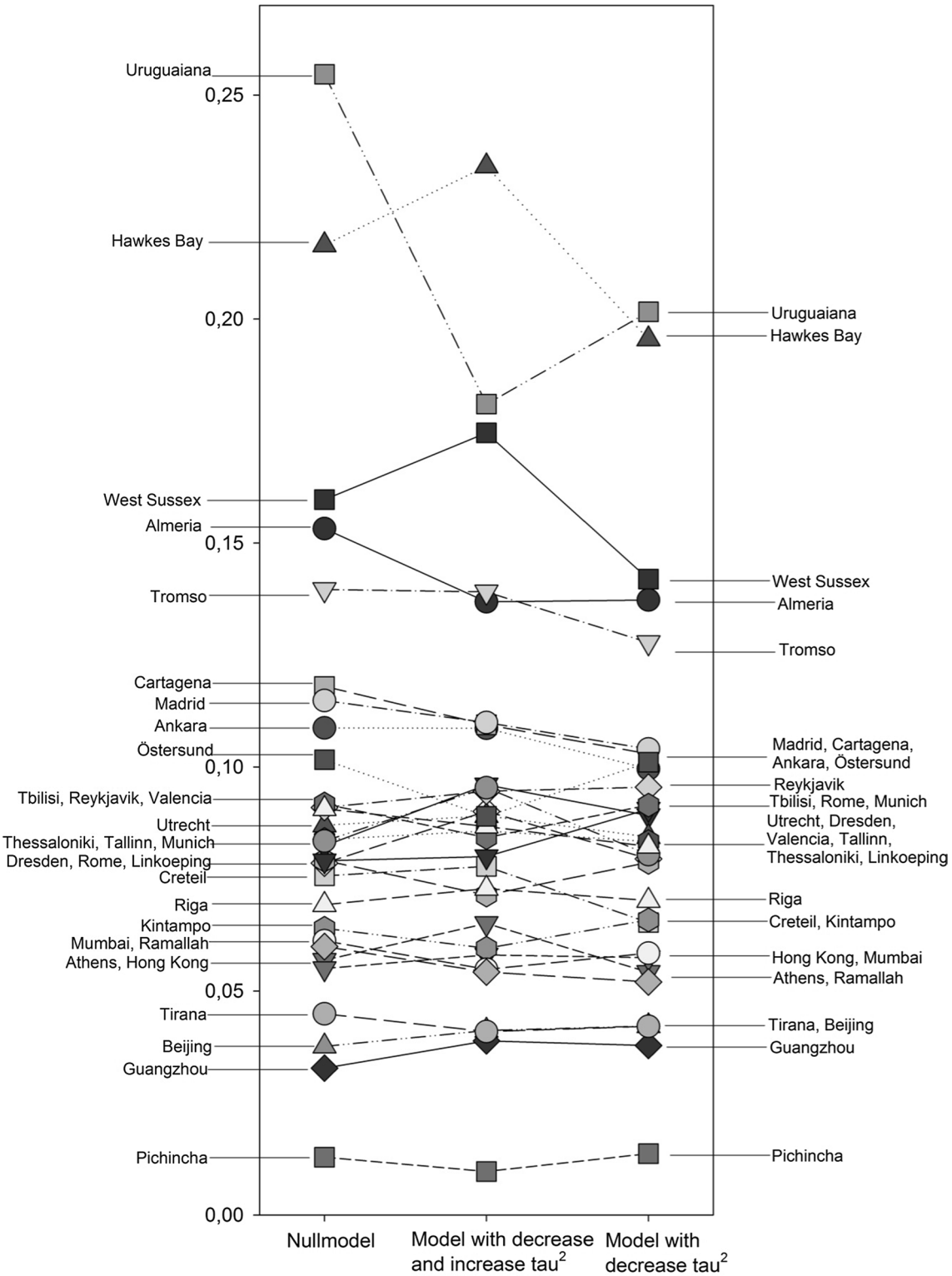

Fig. 1 Predicted prevalence in the centres in the null model and after incorporating the risk factors—for the latter a reference population with risk factor prevalences equal to the arithmetic mean of all centres was used. Model with decrease and increase tau^2: risk factors are included irrespective of the direction of change in the between-centre variance; Model with decrease tau^2: only risk factors that lead to a reduction in the between-centre variance are included for illustrative purpose. (for detailed methods see Online Resource)

Multivariate models

Given the uncertainty regarding estimation of the effect of centre-level variables, we only introduced individual-level variables into the multivariate model. In the model incorporating only variables that resulted in a decrease in between centre variation by 1.5% and more, we obtained a 21% reduction of the between centre prevalence variance tau^2 (Table 3). When risk factors that caused an increase in tau^2 in the univariate models were also introduced, these factors counteracted the influence of factors decreasing tau^2 and the resulting overall change was an increase by 2.4%. The resulting changes in predicted prevalence (converting centre-specific random intercepts from logodds to prevalence) are shown in Fig. 1 (for details of the calculation of the predicted prevalence, see Online Resource).

In the corresponding models for atopic children, we obtained a decrease of tau^2 by 16.8% and an increase of 11.6%, respectively. In non-atopic children, both models yielded a decrease in tau^2, by 27% and 16%, respectively.

Among the 30,703 children in the multivariate model from 29 centres on whom skin prick tests were performed, adjustment for individual environmental factors that decreased tau^2 reduced tau^2 by 23%. Adjusting further for atopy (as measured by skin prick test positivity) increased the reduction in tau^2 to 31%. The corresponding results when all environmental factors (that increased or decreased tau^2) were included were a 9.3% increase before adjustment for atopy and a 0.4% reduction after this adjustment. These tau^2 differentials are broadly consistent with the effect of adjustment for atopy as a single risk factor (8.5% reduction, see above).

Discussion

To our knowledge this is the first analysis investigating the influence of risk factors on the international variation of disease symptoms. Single environmental factors and aeroallergen sensitisation (atopy) measured at the individual (child) level each explained less than 10% of the between-centre variation in wheeze prevalence, and adjustment for some environmental factors accentuated the variation in prevalence. When all the most influential child-level variables were modelled together, the variation in prevalence was little changed (2.4% increase without including atopy, 0.4% decrease if atopy was included).

So far attempts to unravel the influence of risk factors on prevalence differences have been limited to the comparison of two locations [4, 5, 13]. Those studies investigated smaller prevalence differences of 3.7 versus 1.2% [13], 5.8 versus 3.4% [5] and 27 versus 17% [4]. In the Ethiopian study [13], adjusting for housing and mattress material did reduce the magnitude of the OR between rural and urban location for wheeze and sensitization to house dust mite. In the Chinese study [5], the factors that reduced the difference between mainland China and Hong Kong most were foam pillow, cooking with gas, damp housing and raw vegetables. The generalizability of such two centre comparisons is uncertain but in our study we could improve this by analysing 30 diverse study centres.

In such a multi-centre study, the variation in disease prevalence between the centres reflects three components: sampling variation (the play of chance when recruiting individual children); true (non-sampling) variation (between children and between centres) which can be explained by measured risk factors or protective factors which themselves vary in prevalence among the study centres; and true variation between centres which is not (yet) explained. We investigated the changes in this third component (unexplained variation between centres) as different combinations of risk factors or protective factors were included in a multi-level logistic regression model. In such a model, the centre-specific prevalences are reflected by a set of intercepts (logodds) and the parameter tau^2 measures the variance of these centre-specific intercepts.

The individual level environmental and life style factors that caused the highest and most consistent changes in tau^2 were factors related to bedding material, indoor air quality, mostly smoking, and infectious diseases. However, while centre-level variables always result in a decrease of the variation our results illustrate that adjustment for individual risk factors can actually lead to changes in tau^2 in both directions. Overall, individual risk factors explained only a small to moderate amount of the prevalence variation.

Several of the most influential child-level variables leading to changes in tau^2 were potentially prone to reverse causality, if changes had been made to the home environment following (and due to) the onset of asthma or allergy in the child. The bias thereby introduced could be in either direction. For instance, avoidance of pets by allergic families would tend to attenuate a harmful association of pets with wheeze in the child. In contrast, avoidance of feather bedding following the child's asthma diagnosis would accentuate risks associated with synthetic pillows and bedding. Reverse causality is less of a concern for exposures in the first year of life, although selective avoidance by allergic families could still introduce reverse causality biases. Our analyses restricted to children whose parents reported making no such changes are generally reassuring. Except for carpets, the associations with the environmental factors were not affected substantially and making this allowance for possible reverse causality had less effect than the centre selection in this complementary analysis.

Therefore reverse causality does not seem to influence much our broad conclusions regarding the amount of

centre-level variation that could be explained by the investigated environmental factors Nevertheless, these measured factors may actually reflect some other underlying unmeasured risk/protective factor. If the "true" determinant is measured imperfectly, the change in tau^2 will be only partial.

A positive skin prick test resulted in the same variance reduction as the most prominent environmental risk factor. This occurred despite the fact that non-atopic asthma is important worldwide [1] but seems plausible given the strong association of atopy with wheeze within centres and the wide range of atopy prevalence across our study centres. In our previous work, we have found an attributable fraction of atopy on asthma of 40.7% among the affluent centres and 20.3% among the non-affluent centres that already highlighted the importance of atopy on the population level especially for the affluent world [1]. Therefore, risk factors influencing strongly the development of atopy can also be expected to account for some of the international variation in wheeze prevalence, in addition to factors influencing asthma through mechanisms independent of allergy.

In our dataset, ecological risk factors had a considerably greater explanatory potential than individual risk factors, consistent with findings from social sciences regarding the importance of so-called contextual factors. For an epidemiological example, it has been found that the wealth of a neighbourhood has an effect on adult asthma prevalence independently of the individual's socioeconomic status [14] reducing the between centre variation by 37%. For several risk factors in the child's environment one could imagine a similar scenario as children move not only within their homes but are in contact with their friends' and extended families' homes and public locations. For example, it has been shown that community prevalence of cat keeping is a statistically significant determinant of mattress cat allergen levels for non-cat owners [15].

The alternative explanation is that these ecological factors are indicators of different life styles between regions of the world, which would be the underlying overall cause. Indeed, Pearce and Douwes, in their review, propose that there is a Western "package" of environmental and social factors that influence asthma prevalence while there is no known risk factor that would be able to explain on its own either prevalence differences between populations or changes observed within populations over time [16].

In our analysis, the variance explained by average centre-level exposure was generally not diminished when incorporating the corresponding individual-level variable (Online Resource Table E6). We therefore interpret these centre-level correlations as an indirect indication of the potential role of contextual factors, and/or a surrogate for undiscovered individual-level or population-level determinants.

A strength of the present analysis is that it is the first multicentre comparison, made possible by adapting new methodology (i.e. Bauer's scaling method [8]) and therefore being able to compare multilevel logistic regression models that contain different individual risk factors. The study involved a large number of children, therefore the power for investigating individual risk factors is high.

A limitation of our study is that even 30 centres worldwide represent a relatively small number of potential centres especially when investigating centre-level variables and consequently uncertainty around the estimates of between-centre variation is high. When looking at the estimates of tau^2 and its standard error (of the null model), our estimate of 0.32 (SE 0.15) shows similar imprecision to some other studies, e.g. 0.052 (SE 0.026) for the variance in psychiatric health care utilization [17] (235 neighbourhoods) but higher than in other studies, e.g. the study on asthma prevalence in the 287 Chicago neighbourhoods (0.14 (SE 0.02) [18]). This calls for caution when gauging the quantitative importance of the risk factors and part of the changes observed may well lie within the range of uncertainty. To our knowledge, no paper has so far tackled this issue but generally just the percentage of change was reported [14, 17, 19, 20].

Our approach to handling missing observations was a fairly crude one. Unfortunately, almost none of the currently available statistical software offers missing imputation for dichotomous variables in a multilevel framework. However, in sensitivity analyses treating several centres with risk factor information the same as a centre having no information for risk factors, our method to replace the values for all children in the centre with the mean international prevalence proved quite robust i.e. comparable to the original results. Overall, substituting the missing values with mean values is a conservative approach which is expected to lead to an underestimation of the change in variance.

In conclusion, we found several risk factors, both at the individual level and the centre (population) level, that explained part of the large worldwide variation in prevalence of wheeze among children. Overall, individual risk factors explained a moderate amount of the variation in this international study, the most important remediable exposures being bedding material and maternal smoking. Atopy, measured by aeroallergen skin prick tests, also explained a proportion of the worldwide variation in wheeze prevalence. Our multi-centre study design overcomes the limitations of two-centre comparisons and the multi-level modelling approach permits adjustment for the effect of individual-level risk factors, which are excluded in most conventional ecological (centre-level) analyses.

Acknowledgements We wish to thank all children, parents, teachers, field workers and lab workers for their enormous contributions to this collaborative study.

Financial support This work was supported by the German Research Foundation (DFG) (Grant No. WE 4306/3-1).

Appendix: The ISAAC Phase Two Study group

The ISAAC Phase Two Coordinating and Data Centre: S.K. Weiland† (Director), G. Büchele, C. Dentler, A. Jaensch, P. Rzehak, G. Weinmayr (Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany).

The principal investigators: A. Priftanji, A. Shkurti, J. Simenati, E. Grabocka, K. Shyti, S. Agolli, A. Gurakuqi (Tirana, Albania); R.T. Stein, M. Urrutia de Pereira, M.H. Jones, P.M. Pitrez (Uruguaiana, Brazil); P.J. Cooper, M. Chico (Pichincha province, Ecuador); Y.Z. Chen (Beijing, China); N.S Zhong (Guangzhou, China); C.K.W. Lai (National Coordinator), G.W.K. Wong (Hong Kong, China); M-A. Riikjärv, T. Annus (Tallinn, Estonia); I. Annesi-Maesano (Créteil, France); M. Gotua, M. Rukhadze, T. Abramidze, I. Kvachadze, L. Karsanidze, M. Kiladze, N. Dolidze (Tbilisi, Georgia); W. Leupold, U. Keil, E. von Mutius, S.K. Weiland† (Dresden, Germany); E. von Mutius, U. Keil, S.K. Weiland† (Munich, Germany); P. Arthur†, E. Addo-Yobo (Kintampo, Ghana); C. Gratziou (National Coordinator), K. Priftis, A. Papadopoulou, C. Katsardis (Athens, Greece); J. Tsanakas, E. Hatziagorou, F. Kirvassilis (Thessaloniki, Greece); M. Clausen (Reykjavik, Iceland); J.R. Shah, R.S. Mathur, R.P. Khubchandani, S. Mantri (Mumbai, India); F. Forastiere, R. Di Domenicantonio, M. De Sario, S. Sammarro, R. Pistelli, M.G. Serra, G. Corbo, C.A. Perucci (Rome, Italy); V. Svabe, D. Sebre, G. Casno, I. Novikova, L. Bagrade (Riga, Latvia); B. Brunekreef, D. Schram, G. Doekes, P.H.N. Jansen-van Vliet, N.A.H. Janssen, F.J.H. Aarts, G. de Meer (Utrecht, the Netherlands); J. Crane, K. Wickens, D. Barry (Hawkes Bay, New Zealand); W. Nystad, R. Bolle, E. Lund (Tromsø, Norway); J. Batlles Garrido, T. Rubi Ruiz, A. Bonillo Perales, Y. Gonzalez Jiménez, J. Aguirre Rodriguez, J. Momblan de Cabo, A. Losilla Maldonado, M. Daza Torres (Almeria, Spain); L. García-Marcos (National Coordinator), A. Martinez Torres, J.J. Guillén Pérez, A. Piñana López, S. Castejon Robles (Cartagena, Spain); G. García Hernandez, A. Martinez Gimeno, A.L. Moro Rodríguez, C. Luna Paredes, I. Gonzalez Gil (Madrid, Spain); M.M. Morales Suarez-Varela, A. Llopis González, A. Escribano Montaner, M. Tallon Guerola (Valencia, Spain); L. Bråbäck (National Coordinator), M. Kjellman, L. Nilsson, X-M. Mai (Linköping, Sweden); L. Bråbäck, A. Sandin (Östersund, Sweden); Y. Saraçlar, S. Kuyucu, A. Tuncer, C. Saçkesen, V. Sumbulŏglu, P. Geyik, C. Kocabaş (Ankara, Turkey); D.P. Strachan, B. Kaur (West Sussex, UK); N. El-Sharif, B. Nemery, F. Barghuthy, S. Abu Huij, M. Qlebo (Ramallah, West Bank); M. van Hage (IgE analyses - Stockholm, Sweden).

The ISAAC Steering Committee: N. Aït-Khaled (Paris, France); H.R. Anderson and D.P. Strachan* (London, UK); C. Flohr* and H. Williams (Nottingham, UK); F. Forastiere* (Rome, Italy); I. Asher, P. Ellwood, A. Stewart and E. Mitchell (Auckland, New Zealand); J. Crane, N. Pearce and R. Beasley (Wellington, New Zealand); B. Björkstén (Stockholm, Sweden); B. Brunekreef* (Utrecht, the Netherlands); S. Foliaki (Nuku'alofa, Kingdom of Tonga); L. García-Marcos (Murcia, Spain); E. von Mutius* (Munich, Germany); U. Keil (Münster, Germany); S.K. Weiland*†, G. Weinmayr* (Ulm, Germany); C.K.W. Lai and G.W.K. Wong (Hong Kong, China); J. Mallol (Santiago, Chile); S. Montefort (Naxxar, Malta); J. Odhiambo† (Nairobi, Kenya); and C. Robertson (Parkville, Australia).

*Also members of the ISAAC Phase Two Steering Group, †Deceased.

References

1. Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WOC, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. Am J Respir Crit Care Med. 2007;176:565–74.
2. ISAAC Steering Committee I, Beasley R, Keil U, Von Mutius E, Pearce N. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225–32.
3. Weiland SK, Björkstén B, Brunekreef B, Cookson WOC, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. Eur Respir J. 2004;24:406–12.
4. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med. 1994;149:358–64.
5. Wong GWK, Ko FWS, Hui DSC, Fok TF, Carr D, von Mutius E, et al. Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. BMJ. 2004;329:486.
6. ISAAC Steering Comittee. ISAAC Phase Two. http://isaac.auckland.ac.nz/phases/phasetwo/phasetwo.html. Updated 5 Apr 2017. Accessed: 11 Oct 2017.
7. Weinmayr G, Dreyhaupt J, Jaensch A, Forastiere F, Strachan DP. Multilevel regression modelling to investigate variation in disease prevalence across locations. Int J Epidemiol. 2017;46:336–47.
8. Bauer DJ. A note on comparing the estimates of models for cluster-correlated or longitudinal data with binary or ordinal outcomes. Psychometrika. 2008;74:97–105.
9. Richardson DB, Rzehak P, Klenk J, Weiland SK. Analyses of case-control data for additional outcomes. Epidemiology. 2007;18:441–5.
10. Weinmayr G, Gehring U, Genuneit J, Büchele G, Kleiner A, Siebers R, et al. Dampness and moulds in relation to respiratory and allergic symptoms in children: results from Phase Two of the International Study of Asthma and Allergies in Childhood (ISAAC Phase Two). Clin Exp Allergy. 2013;43:762–74.
11. Weinmayr G, Forastiere F, Büchele G, Jaensch A, Strachan DP, Nagel G. Overweight/obesity and respiratory and allergic disease in children: International Study of Asthma and Allergies in Childhood (ISAAC) phase two. PLoS ONE. 2014;9:e113996.

12. García-Marcos L, Castro-Rodríguez JA, Suarez-Varela MM, Garrido JB, Hernandez GG, Gimeno AM, et al. A different pattern of risk factors for atopic and non-atopic wheezing in 9–12-year-old children. Pediatr Allergy Immunol. 2005;16:471–7.
13. Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. Lancet. 1997;350:85–90.
14. Basagaña X, Sunyer J, Kogevinas M, Zock J-P, Duran-Tauleria E, Jarvis D, et al. Socioeconomic status and asthma prevalence in young adults: the European Community Respiratory Health Survey. Am J Epidemiol. 2004;160:178–88.
15. Heinrich J, Bedada GB, Zock J-P, Chinn S, Norbäck D, Olivieri M, et al. Cat allergen level: its determinants and relationship to specific IgE to cat across European centers. J Allergy Clin Immunol. 2006;118:674–81.
16. Douwes J, Pearce N. Asthma and the westernization "package". Int J Epidemiol. 2002;31:1098–102.
17. Ivert AK, Levander MT, Merlo J. Adolescents' utilisation of psychiatric care, neighbourhoods and neighbourhood socioeconomic deprivation: a multilevel analysis. PLoS ONE. 2013;8:e81127.
18. Gupta RS, Zhang X, Sharp LK, Shannon JJ, Weiss KB. The protective effect of community factors on childhood asthma. J Allergy Clin Immunol. 2009;123(1297–1304):e2.
19. Kogan MD, Singh GK, Dee DL, Belanoff C, Grummer-Strawn LM. Multivariate analysis of state variation in breastfeeding rates in the United States. Am J Public Health. 2008;98:1872–80.
20. Merlo J, Ostergren PO, Broms K, Bjorck-Linné A, Liedholm H. Survival after initial hospitalisation for heart failure: a multilevel analysis of patients in Swedish acute care hospitals. J Epidemiol Community Health. 2001;55:323–9.