Urban upbringing and childhood respiratory and allergic conditions: a multi-country holistic study.

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Abstract

Objective: We integratively assessed the effect of different indoor and outdoor environmental exposures early in life on respiratory and allergic health conditions among children from (sub-) urban areas.

Methods: This study included children participating in four ongoing European birth cohorts located in three different geographical regions: INMA (Spain), LISAplus (Germany), GINIplus (Germany) and BAMSE (Sweden). Wheezing, bronchitis, asthma and allergic rhinitis throughout childhood were assessed using parental-completed questionnaires. We designed “environmental scores” corresponding to different indoor, green- and grey-related exposures (main analysis, a-priori-approach). Cohort-specific associations between these environmental scores and the respiratory health outcomes were assessed using random-effects meta-analyses. In addition, a factor analysis was performed based on the same exposure information used to develop the environmental scores (confirmatory analysis, data-driven-approach).

Results: A higher early exposure to the indoor environmental score increased the risk for wheezing and bronchitis within the first year of life (combined adjusted odds ratio: 1.20 [95% confidence interval: 1.13-1.27] and 1.28 [1.18-1.39], respectively). In contrast, there was an inverse association with allergic rhinitis between 6 and 8 years (0.85 [0.79-0.92]). There were no statistically significant associations for the outdoor related environmental scores in relation to any of the health outcomes tested. The factor analysis conducted confirmed these trends.

Conclusion: Although a higher exposure to indoor related exposure through occupants was associated with an increased risk for wheezing and bronchitis within the 1st year, it might serve as a preventive mechanism against later childhood allergic respiratory outcomes in urbanized environments through enhanced shared contact with microbial agents.

Words: 250

Key words

Indoor exposure; microbial load; green space; grey space; asthma; allergic rhinitis

Abbreviations

BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology), GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development), INMA (INfancia y Medio Ambiente; Environment and Childhood), LISAplus (The Influence of Life-Style Factors on the Development of the Immune System and Allergies in East and West Germany plus the Influence of Traffic Emissions and Genetics Study), aOR, 95%CI (adjusted Odds Ratios, 95% Confidence Intervals), NO_2 (Nitrogen dioxide), FA (Factor Analysis),

INTRODUCTION

The prevalence of asthma and allergic conditions is increasing worldwide (1) and has coincided with the rapid and ongoing increase in the percentage of the population residing in urban areas (2). The higher prevalence of asthma and allergic conditions in urban areas compared to the rural areas suggests that urban-related environmental factors may contribute to the pathogenesis of these conditions (3). Previous efforts to evaluate such contributions have mainly focused on a single indoor or outdoor environmental factor (while adjusting for other exposures). In general, there is a plethora of evidence to suggest both positive and negative associations with various indoor and outdoor factors and respiratory health outcomes. Some environmental factors are of particular interest as they demonstrate strong associations with respiratory outcomes (4). For instance, growing up on a farm and thereby having a higher exposure to farm animals, animal feed or unprocessed cow's milk has been shown to protect children from asthma, hay fever and allergic sensitization (5). These associations have been explained by the 'hygiene hypothesis' (6); an early, more intense contact to microbial agents might modulate and program the developing of an immune system towards a non-allergic response (7,8). Much less is known regarding 'beneficial' exposure conditions in urban areas. Nevertheless, previous literature in populations from affluent countries suggests the existence of an inverse association between number of siblings and reported prevalence of allergy-prone diseases, such as hay fever in later childhood due to increased exposure to infections early in life as well as shedding and sharing microbial exposures through more frequent contact (9,10). Further, a recent study among adults observed that a higher proxy for microbial biodiversity in inner city environments, represented by early childhood exposure to pets, day care, bedroom sharing and older siblings, was related to less allergic sensitization (11). Moreover, early exposure to pets, in particular dogs, has been repeatedly suggested to be associated with a reduced risk of (non-atopic) asthma outcomes (12), although overall, associations are inconsistent (13,14). In contrast, associations are rather consistent for exposure to moisture and

mould damage at home in relation to increased risk for asthma and respiratory conditions among children worldwide. Harmful effects of early secondhand tobacco smoke (SHS) exposure in relation to these outcomes have also been documented among children (15,16).

In terms of the outdoor environment, it has been speculated that urbanization leads to a loss of beneficial natural environments which may promote a weakened tolerance against harmful allergens ubiquitous in natural surroundings among children growing up in cities (17,18) as compared to bringing up in rural environments (5,19). Moreover, urban environments are known to vary in their 'grey' surfaces, which comprise industrial, transport and urban-fabric characteristics, often accompanied by an increased exposure to traffic-related air pollution (20,21).

Focusing on only one or very few exposures inadequately captures the complex nature of interrelated environmental factors in real-life and their potentially synergistic/antagonistic impacts on asthma and allergic conditions. To our knowledge, no study has evaluated how a combination of indoor and outdoor environmental factors experienced in early life may affect later respiratory health. Such an approach is certainly needed in order to obtain a holistic perspective of the role of urban upbringing in the pathogenesis of asthma and allergic conditions in different geographic regions. As such, the aim of the present study was to disentangle and prospectively evaluate the association between indicators of urban-related indoor and outdoor environmental exposure characteristics, using a holistic concept, with respiratory and allergic health outcomes in young children from four different birth cohorts established in diverse bio-geographical regions in Europe. Towards this aim, we were particularly interested as to whether we could identify *beneficial* environmental conditions in *urbanized* environments.

MATERIALS AND METHODS

Study population and study area

The study population comprises four ongoing birth cohorts of different bio-geographical regions across southern, central, and northern Europe: INMA (Spain, N=2472), GINIplus (Germany, N=5991), LISAplus (Germany, N=3094), and BAMSE (Sweden, N=4089). For the included studies, approval by the local ethics committees and written consent from participants' families were obtained. A detailed description of these prospective population-based birth cohorts is provided in the **Supplementary Information 1**.

Exposure assessment

We used three different environmental domains that describe the home as well as the surrounding built environment, identically defined and available in each of the participating birth cohorts. For the (1) *a-priori* approach (main analysis), exposure was defined as the Indoor, Grey and Green environmental score (hereafter referred to as "environmental scores"). For the (2) data driven approach (confirmatory analysis), the same exposure data was used in a factor analysis (FA) in order to confirm or falsify the subjectively built environmental scores.

1) A-priori approach (main analysis)

INDOOR environmental score

Based on Campbell and colleagues (11) , the "indoor score" was composed of environmental characteristics associated with suggested higher microbial load ("biodiversity proxy"). These included *family size, number of children, sharing bedroom*, and *pets at home* (11) all of which are suggested to be associated with higher exposure to various microbial agents. The indoor score was calculated from answers to the following four survey questions in the time interval between birth and one year: (1) *"Are there currently pets at home?"* (1 if yes, 0 if no), (2) *"How many (older) children are at*

home (excluding the study child)?" (=1 if ≥ 1, =0 if =0), (3) *"How many persons sleeping in one room together with the study child?"* (=1 if ≥ 1, =0 if =0), and (4) *"How many people live permanently in the household together with the study child (excluding the study child for INMA* (=1 if > 2, =0 if ≤2)*, including the study child for GINIplus, LISAplus, and BAMSE)?"* (=1 if > 3, =0 if ≤3). The combined effect (sum of these scores) was examined together as the cumulative "indoor score" (ranged from 0 to 4).

OUTDOOR-GREEN and OUTDOOR-GREY environmental scores

Outdoor-green environmental score

We used (i) residential surrounding greenness and (ii) neighbourhood green land use to construct our outdoor-green environmental score. The assessment of residential surrounding greenness was based on the satellite-derived Normalized Difference Vegetation Index (NDVI). The NDVI is an indicator of greenness based on land surface reflectance of visible red and near-infrared parts of the spectrum (22). Its values range between –1 and 1, with higher positive numbers indicating more greenness (i.e. photosynthetically-active vegetation). To characterise neighborhood green land use pattern, the CORINE land-cover classes were applied. The CORINE framework, developed by the European Environmental Agency, is a Europe-wide satellite-based inventory of land-cover categorized into 44 classes at a scale of 1:100000 (23) at different levels, last updated in 2011. To define the neighborhood green land use patterns (m^2), the surface area of Level 2 land cover (arable land, forests, heterogeneous agricultural land use types, open spaces with little or no vegetation, pastures, permanent crops, green urban area, sport and leisure facilities and shrub or herbaceous vegetation) within a 300 m buffer around the home address was summed.

For each of the two aspects, a 3-level dummy variable (1 = low, 2 = medium and 3 = high) was created based on tertile values. For GINI/LISA South and BAMSE, the categorization of residential green land use patterns into tertiles was not applicable

because the cut-offs were the same for the first 2 tertiles. Therefore, the median was used as the cut-off (1=lower residential green land use, 2=higher residential green land use). The ”outdoor-green environmental score” was then abstracted by adding the scores for residential surrounding greenness and neighbourhood green land use (ranging from 2 to 5 for GINI/LISA South and BAMSE and 2 to 6 for INMA and GINI/LISA North).

Outdoor-grey environmental score

We applied (i) residential surrounding urban land use, (ii) NO2 levels, and (iii) distance to major road to create outdoor-grey environmental score for each participant. To define residential surrounding urban land use patterns (m^2), the surface area of Level 2 CORINE land cover (includes industrial, commercial units, transport units, and mines) within a 300 m buffer around the home address was summed. Further, within all cohorts we had information on exposure to NO_2 based on existing area-specific land use regression models and applied to the residence around birth. Finally, available harmonized data on distance to major road with constant traffic (in meters) was used (see **Supplementary Table 1**).

As for the outdoor-green score, a 3-level dummy variable (1 = low, 2 = medium and 3 = high) was created based on tertiles of each exposure characteristic. For BAMSE, it was not possible to use tertiles due to the reasons already mentioned above. Thus, two categories were generated based on the median surface area (1=lower residential urban land use, 2=higher residential urban land use). Ultimately, the outdoor-grey environmental score was constructed adding the aforementioned three indicators, which ranged from 3 to 8 for BAMSE and 3 to 9 for the remaining cohorts.

2) Data-driven approach (confirmatory analysis)

The second data-driven approach ("confirmatory analysis") was performed to evaluate the assessment of the environmental scores as well as their associations with the health outcomes. Specifically, the same environmental exposure data as used for building the environmental scores was applied in a factor analysis.

According to the results of the cohort-specific FA, the three selected dimensions explained nearly two-third of the variation (see **Supplementary Table 2**). With respect to all participating birth cohorts, the first dimension was associated with residential surrounding greenness as well as air pollution from traffic ("Greenness/Air pollution"). The second dimension showed high loadings on number of people in the home as well as on whether there are (older) children which we defined as "Crowding". This is comparable to the Indoor Environmental Score, however, it does not include microbial exposure associated with pets. Finally, the third dimension was in particular associated with exposure to pets. For the confirmatory regression analyses, only dimension 1 ("Greenness/Air pollution") and dimension 2 ("Crowding") were considered as comparable to the subjectively built Environmental scores. We nonetheless performed regression analyses with the third dimension ("Pets") as an exposure, but found no significant results with any of the health outcomes tested (data not shown).

Health outcome assessment

We focused on parental completed questionnaire information on (presumably infectious) respiratory outcomes including *wheezing* and *bronchitis* within the first year, as well as on current allergy-prone respiratory outcomes *asthma* and *allergic rhinitis / hay fever* in later childhood (INMA: 7y, GINI/LISA south and north: 6y, BAMSE: 8y). For all cohorts except for INMA, there were further data available on atopic status (specific immunoglobulin E (IgE) > 0.35 kU/l) at 6 and 8 years, respectively. Detailed information of the health outcome assessment in the birth cohorts is provided in the **Supplementary Table 3**.

Statistical analysis

Cohort-specific logistic regression models (24) were applied to analyze the associations between (1) the environmental scores (main analysis) as well as the (2) identified dimensions of the FA (confirmatory analysis, **Supplementary Information 3** and **Supplementary Table 2**) with each of the respiratory and allergic health outcomes at age 1 and between 6-8 years, respectively. Random-effects meta-analysis (25) was used to calculate combined estimates to allow for potential between–cohort heterogeneity. Based on previous literature, the regression models of the main analysis (environmental scores) were adjusted for sex, maternal education, maternal allergy, maternal smoking during pregnancy, breastfeeding, exposure to environmental tobacco smoke at home (first year), dampness at home (first year) and cohort (INMA: Asturias, Gipuzkoa, Sabadell, Valencia, child belongs to either GINIplus or LISAplus). The regression models of the confirmatory analysis were mutually adjusted for the identified dimensions in addition to the variables mentioned above for the main analysis. All results are presented as odds ratios (OR) with corresponding 95% confidence intervals (95%-CI).

Sensitivity and stratified analyses

With respect to the main analyses, we first evaluated whether the effects were more pronounced among atopic children with asthma or allergic rhinitis/hay fever. This was only possible in GINI/LISA South, GINI/LISA North and BAMSE. In addition, we added "dampness" (1=yes, 0=no, all birth cohorts) and "attending daycare" before the second birthday (1=yes, 0=no, INMA and BAMSE), a further source of possible microbial exposure to the indoor score for all cohorts. Lastly, we performed another FA and additionally included "dampness" as well as "passive smoke" exposure during the first year of life.

All statistical analyses were performed using the statistical software R, version 3.4.0 (26) (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/), using FAmix within the "PCAmixdata" package for factor analysis (27).

RESULTS

Study population and environmental scores

The study population and exposure characteristics are displayed in **Table 1**. The cohort-specific distribution of the environmental scores can be found in **Supplementary figure 1**.

Main analysis: Associations between environmental scores and health outcomes

Overall, as displayed in **Table 2**, a higher indoor environmental score, was found to increase the risk for wheezing and bronchitis outcomes within the first year of life in adjusted random-effects meta-analyses (aOR 1.20 [1.13-1.27] and 1.28 [1.18-1.39], respectively). In contrast, we observed statistically significant inverse associations between a higher indoor environmental score with allergic rhinitis in later childhood (0.93 [0.85-1.02] and 0.85 [0.79-0.92], respectively). For the remaining environmental scores, no statistically significant associations were obtained.

There were no major differences in the results when the analyses were stratified by atopic status, except that there was a slightly more pronounced inverse effect between exposure to the indoor score and allergic rhinitis among atopic children (0.85 [0.76-0.95]) compared to the non-atopic children (0.83 [0.64-1.06], **Supplementary Table 4**). Further, including "dampness" and "daycare before the second birthday" as additional sources of microbial exposure to the indoor score did not change the magnitude or direction of the effect estimates for any of the outcomes tested (data not shown).

Confirmatory analysis (Factor analysis)

The procedure as well as the cohort-specific results of the FA are presented in the **Supplementary Information 3** and **Supplementary Table 2**. The FA identified three environmental dimensions: 1. “Outdoor exposure”, 2. “Crowding”, and 3. “Pets”. For the dimension “Crowding” (high factor loadings for “number of people at home” and “number of (older) children”), we found similar associations in relation to the health outcomes as it was observed with the indoor environmental score in mutually adjusted regression analyses (**Table 3**). “Crowding” at home significantly increased the risk for wheezing and bronchitis within the first year (1.20 [1.15-1.26] and 1.27 [1.19-1.36], respectively) but was inversely associated with childhood asthma and allergic rhinitis (0.91 [0.85-0.98] and 0.87 [0.81-0.93], respectively). In contrast, the factor described by “outdoor exposure” significantly increased the risk for bronchitis within the first year (1.04 [1.00-1.07]), but there was no significant associations with asthma and allergic rhinitis in later childhood. Lastly, we further included “dampness within the first year” and “passive smoke exposure within the first year” in the FA, but all results were unchanged. There were no statistically significant associations between the third dimension identified in the FA (related to pets) with any of the health outcomes tested (data not shown).

DISCUSSION

To the best of our knowledge, this study is the first to specifically consider early life environmental exposures in relation to respiratory and allergic outcomes using a holistic approach that integrates several relevant indoor and outdoor exposure characteristics across different geographical regions. We observed that a higher suggested microbial load indoors was associated with increased risk for infection prone wheezing and bronchitis within the first year of life. This exposure, on the other hand, was associated with a decreased risk of allergic rhinitis in later childhood, which highlights the importance

of longitudinal studies for assessing health effects from certain exposures. No consistent results were observed for the outdoor-related green and grey environmental scores. The results of the a-priori based indoor environmental score were confirmed by a data-driven approach, in which a “crowding” dimension was identified. For the outdoor grey and green environmental scores, the results of the FA indicated that the outdoor environment cannot be easily considered as isolated environmental dimensions in relation to health, but are rather highly interrelated.

Studies have suggested that lifestyles associated with early exposures to farm and rural environments may be associated with higher and diverse microbial exposures, and that this might in turn lower the risk of allergic immune responses later in childhood and adulthood (28,29). The indoor and outdoor related microbial profile in *urban* environments might differ considerably from those in rural areas, in terms of levels, composition, and diversity (30), and therefore might also have different effects on allergic outcomes.

Lower prevalences of hay fever and allergic sensitization have also been consistently observed with a higher number of (older) siblings in urban areas (9,10). Family size or more frequent human contact in general is suggested to be a source of higher microbial and viral exposure through shedding and sharing (6,31). According to the “hygiene hypothesis” (6), this might have the potential to attenuate the harmful effects of increased hygienic conditions and lower xenogeneic pressure associated with a “Westernized” life style on the maturating immune system, resulting in increased risks for allergy prone diseases in urban environments. In fact, although we here consistently observed that a higher suggested microbial and viral load indoors (through occupants) around birth was strongly associated with a higher risk of infections during the first year of life, this association was reversed for asthma and allergic rhinitis later in childhood. Further, for two out of four participating birth cohorts, sizeable inverse associations with allergic

rhinitis were also found when we additionally included daycare attendance before the second birthday in the calculation of the indoor score. A recent urban birth cohort study in the U.S. observed a bi-directional relationship between cumulative early day care attendance with asthma, pointing out a reduced risk for asthma with increased duration of daycare attendance (> 1800 hours) (32). Further, previous studies looking at the health effects of early higher exposure to microbial components in *urban* settled house dust (most prominently, floor and mattress dust) are also partly in line with our findings for asthma and allergic rhinitis.

According to the available literature, higher and more diverse microbial loads indoors have been associated with lower risks for allergic outcomes in a few small-scale studies (33–35). Lastly, the combination of a large family size and exposure to farming was especially associated with a remarkable decrease in hay fever (36). However, it was not possible to disentangle the effects of both protective factors, suggesting two different biological mechanisms and pointing out the magnitude of both environmental determinants in relation to allergy prone diseases.

Our results indicate an important signal of *human* derived and transferred microbial and viral exposure in homes in relation to early respiratory infections and childhood allergic rhinitis. These effects appeared more important that those related to outdoor characteristics. Though “crowding” has been also suggested to be a risk factor for hospitalization in childhood and viral infections are the major cause of acute wheezing exacerbation in early life (37), viral respiratory infections are very common. For most children, no negative impact in later life is expected – unless they are impaired by host factors or deficiencies in the innate immune response to these agents (38). We also included “exposure to pets” in the indoor environmental score, however, “crowding”, as identified by the factor analysis, was exclusively based on person associated factors.

Previous dust microbiome studies suggested that bacterial exposure in urban settings is generally largely dominated by occupants and to a lesser extent by pets, and not by outdoor sources (39–41). A study in over 500 children living in the inner city environments of Baltimore, Boston, New York, and St Louis, United States, observed that a concomitant high exposure to bacteria in dust (Firmicutes and Bacteriodetes) and allergens might reduce the risk for atopy and recurrent wheezing (35). On the other hand, a recent investigation among 189 children from the German LISAplus study was not able to confirm protective findings of bacterial exposure in relation to atopy and wheezing. Rather, associations were found with a higher and more diverse fungal exposure assessed in living-room floor dust samples (34). Unfortunately, at present, current knowledge remains limited as to which microbial markers in dust may be associated with a decreased risk for asthma and allergic outcomes via a mechanism that involves greater family size or more frequent human contact.

It is assumed that indoor microbial communities are part of the closer neighborhood and built environment (42). Therefore, the simultaneous exposure to indoor and outdoor environmental exposures might play even a more important role for metropolitan areas compared to rural areas due to a presumably more heterogeneous exposure profile of coincident hazardous and protective factors (18,43). While there remained a consistent strong inverse association between exposure to suggested higher microbial load indoors, as determined by the indoor score and “crowding”, on later asthma and allergic rhinitis outcomes in all sensitivity analyses, the associations were less coherent for the remaining environmental exposure constructs.

In general, compared to natural surroundings, artificial green urban areas can also be potential sources of harmful allergen exposure (44,45). Fundamentally, it is likely that associations with respiratory and allergic health will depend on the allergenicity of the respective green exposure surrounding the participants (19,46,47). Moreover, the

contextual factors describing the outdoor environment are highly area-specific and a more detailed exposure characterization would be desirable. Unfortunately, this was not possible for the current publication as the aim was to capture a wide geographical region and the exposure characteristics were restricted to those commonly available.

Future studies which consider region-specific outdoor characteristics at a finer scale are therefore recommended (48). In summary, the results of our study underline the importance of early exposure to *indoor* related characteristics in comparison to outdoor related characteristics with respect to respiratory and allergic health outcomes in urbanized residential surroundings.

A key strength of this study is its comprehensive approach, integrating indoor as well as outdoor environmental exposures in relation to respiratory and allergic health outcomes. Other advantages were the large sample size of the birth cohorts, the harmonized exposure and health outcome assessments, information on several important confounders and the inclusion of regions across the north, center, and south of Europe.

Limitations of the study include the fact that we could not consider further potentially relevant (built) environment factors such as the school environment, which may act as additional source of regular microbial exposure. In addition, although we had in a large part harmonized exposure and health outcome information across all birth cohorts, we only included exposures which were available and identically assessed in all study populations which might have led to an unknown amount of information loss. Unfortunately, an identical health outcome assessment was not possible due to regional differences within the populations. In this context, we also did not have data on the *actual* microbial exposure, e.g. as determined in dust samples, associated with the respective environmental exposure domains. For the indoor environmental domain in the main analyses, we only focused on suggested higher microbial load exposure and excluded

potential harmful exposures such as dampness and passive smoke exposure. Nevertheless, all statistical models were adjusted for dampness as well as passive and *in utero* tobacco smoke exposure. Apart from that, including more sources related to hazardous exposure characteristics in the FA did neither change the “dimensions” assignment, nor result in a coherent third exposure dimension. Lastly, although infections are crucial in the pathogenesis of allergic diseases and a more accurate information by serology or culture would be desirable, we have to rely on parental reported diseases.

Conclusion

Our study indicates that, in particular early exposure to a suggested higher microbial load indoors is associated with an increased risk of presumably infection-prone wheezing and bronchitis in early childhood but with a decreased risk for asthma and allergic rhinitis later in childhood. There were no coherent findings for exposure to outdoor related environmental factors, which highlights the importance of indoor related factors in early life over outdoor related sources in adjusted analyses. The assumed biological mechanism might be an early and more intense encounter with viruses and higher microbial load associated with greater family size. If specific exposure can be identified, e.g. obtained through dust samples in homes with greater family size or daycare centers, this might serve substantial preventive capability.

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Contributions

Conception and design: CT, PD, JS, XB, JMA

Analysis and interpretation: CT, XB, PD, JS

Critical revising the manuscript and allocation of data: CT, JS, LC, EF, AB, OG, EM, DB, JH, SK, IM, MS, DS, LC, ME, AFS, AF, JI, AL, AT

Conflict(s) of Interest

None.

Ethics committee approval

For the included studies, approval by the local ethics committees and written consent from participants' families were obtained.

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Table 1: Study population characteristics, exposure and health outcome information by birth cohort

	INMA (N=2472)	GINI/LISA South (N=4413)	GINI/LISA North (N=3390)	BAMSE (N=4089)
HEALTH OUTCOMES				
Wheezing 1st year	36%	15%	17%	15%
Bronchitis 1st year	18%	15%	19%	8%
Asthma (6-8 years)	7y: 6%	6y: 3%	6y: 3%	8y: 6%
Asthma/IgE+	-	46%	38%	50%
Asthma/IgE-	-	19%	30%	32%
Asthma/wheeze 1st year	7%	5%	3%	10%
Asthma/no wheeze 1st year	3%	2%	2%	4%
Asthma/bronchitis 1st year	7%	4%	4%	7%
Asthma/no bronchitis 1st year	5%	2%	2%	5%
Allergic rhinitis (6-8 years)	7y: 4%	6y: 7%	6y: 6%	8y: 6%
Allergic rhinitis/IgE+	-	53%	38%	74%
Allergic rhinitis/IgE-	-	9%	20%	9%
Allergic rhinitis /wheeze 1st year	4%	7%	7%	6%
Allergic rhinitis /no wheeze 1st year	3%	5%	3%	5%
Allergic rhinitis /bronchitis 1st year	5%	6%	7%	5%
Allergic rhinitis /no bronchitis 1st year	3%	5%	3%	5%
IgE aero-allergens (6-8 years)	-	6y: 31%	6y: 26%	8y: 26%
EXPOSURE INDOOR				
Pets at home	32%	21%	26%	19%
(Older) children at home	42%	44%	56%	44%
Number of people at home: ≥ 3 people (including child)	47%	44%	56%	44%
Sharing bedroom	45%	72%	51%	93%
Dampness at birth	10%	7%	4%	24%
Daycare before 2nd birthday	35%	-	-	72%
OUTDOOR grey and green (median)				
NDVI 100m buffer	0.25	0.30	0.30	0.22
Green index 300m buffer (m²)	69330	3665	84530	0
Grey index 300m buffer (m²)	193000	278800	198000	282600
NO_2 (µg/m³)	26.95	21.04	23.25	12.43
Distance to major road with permanent traffic (m)	50	177	338	120
CO-VARIATES				
Female sex	49%	48%	49%	49%
Maternal education:				
Low	23%	13%	22%	9%
Medium	42%	29%	48%	50%
High	36%	59%	30%	41%
Maternal allergy	26%	40%	28%	41%
Maternal smoking during pregnancy	18%	9%	13%	13%
Any breastfeeding	85%	69%	41%	98%
Dampness 1st year	10%	7%	4%	24%
Passive smoke 1st year	47%	16%	30%	19%
Cohort	Asturias: 20% Gipuzkoa: 25% Sabadell: 31% Valencia: 24%	GINI: 67% LISA: 33%	GINI: 90% LISA: 10%	-

Table 2: Exposure to environmental scores (indoor, grey ad green) and **early wheezing and bronchitis** within the 1st year, stratified by cohort and total effect (Random effects model)*.

		Wheezing 1st year	Bronchitis 1st year	Asthma 6-8 years	Allergic Rhinitis 6-8 years
Indoor Score	INMA	1.14 (1.06-1.22)	1.14 (1.04-1.25)	7y: 0.89 (0.76-1.05)	7y: 0.83 (0.68-1.01)
	GINI/LISA South	1.26 (1.15-1.38)	1.38 (1.26-1.52)	6y: 0.89 (0.73-1.09)	6y: 0.83 (0.73-0.95)
	GINI/LISA North	1.26 (1.16-1.40)	1.31 (1.20-1.43)	6y: 0.89 (0.70-1.13)	6y: 0.93 (0.79-1.10)
	BAMSE	1.14 (1.04-1.25)	1.29 (1.14-1.46)	8y: 1.01 (0.87-1.17)	8y: 0.83 (0.71-0.97)
	Total	**1.20 (1.13-1.27)**	**1.28 (1.18-1.39)**	0.93 (0.85-1.02)	**0.85 (0.79-0.92)**
Grey Score	INMA	1.07 (1.00-1.14)	1.00 (0.92-1.09)	7y: 1.07 (0.93-1.24)	7y: 1.17 (0.98-1.39)
	GINI/LISA South	0.99 (0.94-1.05)	0.98 (0.93-1.04)	6y: 0.96 (0.85-1.09)	6y: 0.93 (0.86-1.01)
	GINI/LISA North	1.03 (0.97-1.09)	1.00 (0.95-1.06)	6y: 0.98 (0.85-1.14)	6y: 1.01 (0.91-1.13)
	BAMSE	1.00 (0.95-1.06)	1.00 (0.93-1.08)	8y: 0.86 (0.78-0.94)	8y: 0.88 (0.80-0.97)
	Total	1.02 (0.99-1.05)	1.00 (0.96-1.03)	0.96 (0.87-1.06)	0.97 (0.89-1.07)
Green Score	INMA	0.98 (0.90-1.06)	1.03 (0.93-1.15)	7y: 0.84 (0.70-1.00)	7y: 0.81 (0.65-1.00)
	GINI/LISA South	1.03 (0.93-1.14)	0.98 (0.89-1.09)	6y: 0.96 (0.76-1.21)	6y: 1.07 (0.92-1.25)
	GINI/LISA North	1.01 (0.93-1.09)	1.02 (0.94-1.09)	6y: 1.01 (0.83-1.22)	6y: 1.00 (0.87-1.16)
	BAMSE	1.00 (0.91-1.10)	0.96 (0.85-1.09)	8y: 1.22 (1.05-1.43)	8y: 1.14 (0.98-1.34)
	Total	1.00 (0.96-1.05)	1.00 (0.96-1.05)	1.00 (0.84-1.19)	1.01 (0.89-1.15)

*Adjusted for: sex, cohort, maternal allergy, maternal smoking during pregnancy, maternal education, breastfeeding, dampness at home 1st year, exposure to passive smoke 1st year.

Table 3: Exposure to environmental dimensions ("Outdoor exposure" and "Crowding") as identified by factor analysis and health outcomes, stratified by cohort and total effect (Random effects model)*.

		Wheezing 1st year	Bronchitis 1st year	Asthma 6-8 years	Allergic Rhinitis 6-8 years
DIM 1	INMA	0.98 (0.92-1.05)	1.07 (0.96-1.17)	7y: 0.93 (0.80-1.07)	7y: 0.83 (0.70-1.00)
„Outdoor exposure"	GINI/LISA South	1.02 (0.96-1.09)	1.04 (0.98-1.11)	6y: 1.05 (0.93-1.18)	6y: 1.03 (0.94-1.11)
	GINI/LISA North	1.02 (0.96-1.08)	1.03 (0.97-1.09)	6y: 1.00 (0.87-1.15)	6y: 0.94 (0.85-1.05)
	BAMSE	1.03 (0.97-1.10)	1.02 (0.94-1.11)	8y: 1.13 (1.03-1.23)	8y: 1.07 (0.97-1.17)
	Total	1.01 (0.98-1.05)	**1.04 (1.00-1.07)**	1.04 (0.96-1.13)	0.99 (0.91-1.07)
DIM 2	INMA	1.15 (1.08-1.23)	1.16 (1.07-1.25)	7y: 0.91 (0.79-1.05)	7y: 0.85 (0.71-1.01)
„Crowding"	GINI/LISA South	1.23 (1.15-1.32)	1.33 (1.24-1.42)	6y: 0.85 (0.72-1.00)	6y: 0.84 (0.75-0.93)
	GINI/LISA North	1.27 (1.17-1.37)	1.34 (1.24-1.44)	6y: 0.89 (0.74-1.07)	6y: 0.95 (0.83-1.08)
	BAMSE	1.16 (1.08-1.25)	1.28 (1.16-1.41)	8y: 0.96 (0.86-1.09)	8y: 0.85 (0.75-0.96)
	Total	**1.20 (1.15-1.26)**	**1.27 (1.19-1.36)**	**0.91 (0.85-0.98)**	**0.87 (0.81-0.93)**

*Adjusted for: sex, cohort, maternal allergy, maternal smoking during pregnancy, maternal education, breastfeeding, dampness at home 1st year, exposure to passive smoke 1st year, and environmental dimensions.

Supplementary Data

Supplementary Information 1: Description of the study population

The ***INMA*** (INfancia y Medio Ambiente; Environment and Childhood) birth cohort is a network of population-based birth cohorts across Spain, which aims to study the impact of environmental factors on pregnancy outcomes, child growth and development. Our study used data from four INMA study centers, Asturias (recruited from May 2004 to July 2007, N=485), Gipuzkoa (recruited from April 2006 to January 2008, N=623), Sabadell (recruited from July 2004 to July 2006, N=771) and Valencia (recruited from November 2003 to June 2005, N=593). Detailed information on the cohorts and data collection processes have been published elsewhere (www.proyectoinma.org) (1).

GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) (2) and ***LISAplus*** (The Influence of Life-Style Factors on the Development of the Immune System and Allergies in East and West Germany plus the Influence of Traffic Emissions and Genetics Study) (3,4) are two ongoing population-based birth cohorts in Germany. Briefly, healthy full-term neonates with a normal birth weight were recruited at selected maternity hospitals. For the current investigation, only LISAplus children from Munich and Wesel were included as the complete environmental exposure information was only available for these study areas (n = 1812). The GINIplus cohort (*n* = 5991) was recruited in Munich and Wesel between 1995 and 1998, while the LISAplus cohort (*n* = 3094) was recruited in Munich, Leipzig, Wesel and Bad Honnef between 1997 and 1999. GINIplus consists of two study groups: one is an observation group and the second is an intervention group who received a nutritional intervention during the first 4 months of life. In the intervention group, a double-blind controlled trial compared the effect of three hydrolysed formulas vs. cow's milk on allergy development. Newborns with a family history of allergy were invited for the intervention

group. Participants with a negative family history or a positive family history but who declined to participate in the intervention trial were included in the observation group. As the GINIplus and LISAplus birth cohorts have similar study designs, data were pooled and are presented per study area (GINI/LISA South for the Munich area, *n* = 4413 and GINI/LISA North for the Wesel area, *n* = 3390).

The ***BAMSE*** (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) study is a longitudinal population-based birth cohort in which infants were recruited at birth and prospectively followed during childhood and adolescence. A total of 4089 infants born in Stockholm, Sweden, between 1994 and 1996 were included. At a median infant age of 2 months, parents completed the baseline questionnaire which assessed environmental exposures, parental smoking habits, residential characteristics, lifestyle, and parental allergies (5). Repeated follow-ups were carried out at 1, 2, 4, and 8 years, and parents filled in similar questionnaires with a main focus on the children's symptoms related to wheezing and allergic diseases, but information on various exposures was collected as well. The response rates were 96%, 94%, 91%, and 84%, respectively. Blood was obtained from 2614 (64%) and 2480 (61%) of the children at the age of 4 and 8 years, respectively. The study was approved by the ethical committee of Karolinska Institutet.

Supplementary Table 1: Cohort-specific questions used for defining the environmental scores

INMA	
Indoor	1. 1st year: *Do you or did you have animals at home since the birth of the child? (yes/no)* 2. 1st year: *The child sleeps currently: alone / together with other persons* 3. 3rd trimester: *Are there children younger than 12 year living in your home? (yes/no)* 4. 1st year: *How many people live together with your child? (numeric)* *5. 1st year: Is your child visiting daycare? (no, yes-some hours, yes=full time)* *6. 3rd trimester: In your home, are there any signs of dampness? (combined: yes/no living-room / bedroom)*
Outdoor-green	1. Residential surrounding greenness (NDVI) 100m buffer: *Landsat 4–5 Thematic Mapper (TM) data at 30 m × 30 m resolution* (6,7) *were used, obtained from the Global Visualization Viewer of the U.S. Geological Survey (2011). The Landsat TM data for INMA were acquired for the year 2007, which corresponds to the middle of the data collection period of the cohort* (6) *(2004–2008). For each participant, mean NDVI values in 100 m buffers around the place of residence at the time of birth were calculated* (8,9). 2. Green Index 300m buffer around the residential address
Outdoor-grey	1. Grey Index 300m buffer around the residential address (numeric) 2. NO_2 exposure around birth (numeric) *Existing area-specific land use regression (LUR) models, applied to the residence during the first year of life in INMA* (10). 3. Distance to nearest major road with permanent traffic (numeric)
GINIplus	
Indoor	1. 1st year: *Do you currently have pets in the home (first 4 months since birth)? (yes/no)* 2. 1st year: *In the first 4 months since birth, how many persons slept together in a room with the child? (numeric)* 3. 1st year: *How many persons belong to your household? (numeric), including the study child* 4. 1st year: *How many persons (children) belong to your household? (numeric), including the study child* 5. 1st year: *In the first 4 months since birth, who took care of the child? (at home / at the grand parents / daycare)* (not applicable, only a few children in daycare) 6. 1st year: *Would you consider your flat as damp? (yes/no)*
Outdoor-green	1. Residential surrounding greenness (NDVI) 100m buffer: *Landsat 4–5 Thematic Mapper (TM) data at 30 m × 30 m resolution were used, obtained from the Global Visualization Viewer of the U.S. Geological Survey (2011). The Landsat TM data for GINIplus were acquired for the year 1998, which corresponds to the time of the recruitment of the cohort (1995–1998). For each participant, mean NDVI values in 100 m buffers around the place of residence at the time of birth were calculated* (11). 2. Green Index 300m buffer around the residential address
Outdoor-grey	1. Grey Index 300m buffer around the residential address (numeric)

	2. NO_2 exposure at birth (numeric) *Existing area-specific land use regression (LUR) models, applied to the residence at the time of birth* (12). 3. Distance to nearest major road with permanent traffic (numeric)
LISAplus	
Indoor	1. 3 months: *Do you currently have pets at home? (yes/no)* 2. 3 months: *In the first 3 months since birth, how many persons slept together in a room with the child? (numeric)* 3. 3 months: *How many persons belong to the household (including the study child)? (numeric)* 4. 3 months: *Number of children in the household (including the study child) (numeric)* 5. 3 months: *Would you consider your flat as damp? (yes/no)*
Outdoor-green	1. Residential surrounding greenness (NDVI) 100m buffer *Landsat 4–5 Thematic Mapper (TM) data at 30 m × 30 m resolution were used, obtained from the Global Visualization Viewer of the U.S. Geological Survey (2011). The Landsat TM data for LISAplus were acquired for the year 1998, which corresponds to the time of the recruitment of the cohort (1998–1999). For each participant, mean NDVI values in 100 m buffers around the place of residence at the time of birth were calculated* (11). 2. Green Index 300m buffer around the residential address
Outdoor-grey	1. Grey Index 300m buffer around the residential address (numeric) 2. NO_2 exposure at birth (numeric) *Existing area-specific land use regression (LUR) models, applied to the residence at the time of birth* (12). 3. Distance to nearest major road with permanent traffic (numeric)
BAMSE	
Indoor	1. Birth: *Are there pets in the home? (yes/no)* 2. Birth: *How many people does the child share a bedroom with? (numeric)* 3. Birth: How many people are permanent residents in the same dwelling as the child, including the child? Adults (18 years and over) / Children 0-2 years old / Children 3-12 years old) / Teenagers 13-17 years 4. Birth: How many people are permanent residents in the same dwelling as the child, including the child? Children 0-2 years old / Children 3-12 years old) / Teenagers 13-17 years 5. 2nd year: *What type of child care does your child have? 1 = Day nursery / 2 = Child-minder or other person (e.g. relative, sitter) who cares for the child in his/her own home 3 = Nanny or other person (e.g. relative, sitter) who cares for the child in the child's own home 4 = At home with parent (1=day nursery / 0=other types)* 6. Birth: *Is there, or has there ever been, any type of moisture damage (spots and the like) in the home? (yes/no)*
Outdoor-green	1. Residential surrounding greenness (NDVI) 100m buffer *The assignment of NDVI to the home addresses of all cohort participants was done using a harmonized method previously described* (11). *For each participant, mean NDVI values in 100 m buffers around the place of residence at the time of birth were calculated.*

	2. Green Index 300m buffer around the residential address
Outdoor-grey	1. Grey Index 300m buffer around the residential address (numeric) 2. NO_2 exposure at birth (numeric) *NO2 concentrations were derived from area-specific land-use regression models as part of the European Study of Cohorts for Air Pollution Effects project for the European cohorts* (13) (Gruzieva et al. 2013). 3. Distance to nearest major road with permanent traffic (numeric)

Supplementary Information 2: Data driven approach (Factor Analysis)

The second approach ("confirmatory analysis") was performed in order to evaluate the findings based on the environmental scores with a data-driven-approach by using a Factor Analysis (FA). Hence, the same environmental exposure data as it was used for building the environmental scores was applied. The information on indoor and outdoor exposure available within the participating birth cohorts are described by a mixture of categorical and numeric variables. Therefore, we used the Factor Analyses (FA) of mixed data (FAmix) within the "PCAmixdata" R package and a orthogonal rotation (14) which incorporates qualitative and quantitative data. In order to be consistent with the subjectively built Environmental Scores, we a-priori selected three dimensions (dim) which are based on the scores describing the association of the exposure variables with the created dimensions. According to the results of the cohort-specific FA, the three selected dimensions explained nearly two-third of the variation (see **Supplementary Table 2**). With respect to all participating birth cohorts, the first dimension was associated with residential surrounding greenness as well as air pollution from traffic ("Greenness/Air pollution"). The second dimension showed high loadings on number of people in the home as well as on whether there are (older) children which we defined as "Crowding". This is comparable to the Indoor Environmental Score, however, it does not include microbial exposure associated with pets. Finally, the third dimension was in particular associated with exposure to pets. For the confirmatory regression analyses, only dimension 1 ("Greenness/Air pollution") and dimension 2 ("Crowding") were considered as comparable to the subjectively built Environmental scores. We nonetheless performed regression analyses with the third dimension ("Pets") as an exposure, but found no significant results with any of the health outcomes tested (data not shown).

Supplementary Table 2: Cohort-specific Factor analysis, only factor loadings ≥ 0.3 are shown

INMA (N=1974)

	Dimension 1 ("Outdoor exposure") Explained variance: **32%**	**Dimension 2** ("Crowding") Explained variance: **21%**	**Dimension 3** ("Pets") Explained variance: **12%**
NDVI 100m buffer	**0.64**		
Green index	**0.84**		
NO2 birth	**0.53**		
Grey index	**0.82**		
Distance to major road			
(Older) children at home		**0.81**	
Nr of people at home		**0.84**	
Sharing bedroom		**0.30**	
Pets at home			**0.59**

GINI/LISA south (N=3446)

	Dimension 1 ("Outdoor exposure") Explained variance: **31%**	**Dimension 2** ("Crowding") Explained variance: **21%**	**Dimension 3** ("Pets") Explained variance: **10%**
NDVI 100m buffer	**0.42**		
Green index	**0.78**		
NO2 birth	**0.54**		
Grey index	**0.79**		
Distance to major road	**0.33**		
(Older) children at home		**0.90**	
Nr of people at home		**0.90**	
Sharing bedroom			**0.30**
Pets at home			**0.65**

GINI/LISA north (N=2606)

	Dimension 1 ("Outdoor exposure") Explained variance: **33%**	**Dimension 2** ("Crowding") Explained variance: **21%**	**Dimension 3** ("Pets") Explained variance: **11%**
NDVI 100m buffer	**0.59**		
Green index	**0.85**		
NO2 birth	**0.46**		
Grey index	**0.86**		
Distance to major road	**0.32**		
(Older) children at home		**0.89**	
Nr of people at home		**0.89**	
Sharing bedroom			
Pets at home			**0.76**

BAMSE (N=3984)

	Dimension 1 ("Outdoor exposure") Explained variance: **33%**	**Dimension 2** ("Crowding") Explained variance: **21%**	**Dimension 3** ("Pets") Explained variance: **11%**
NDVI 100m buffer	**0.50**		
Green index	**0.68**		
NO2 birth	**0.58**		
Grey index	**0.67**		
Distance to major road			
(Older) children at home		**0.80**	
Nr of people at home		**0.80**	
Sharing bedroom			**0.41**
Pets at home			**0.31**

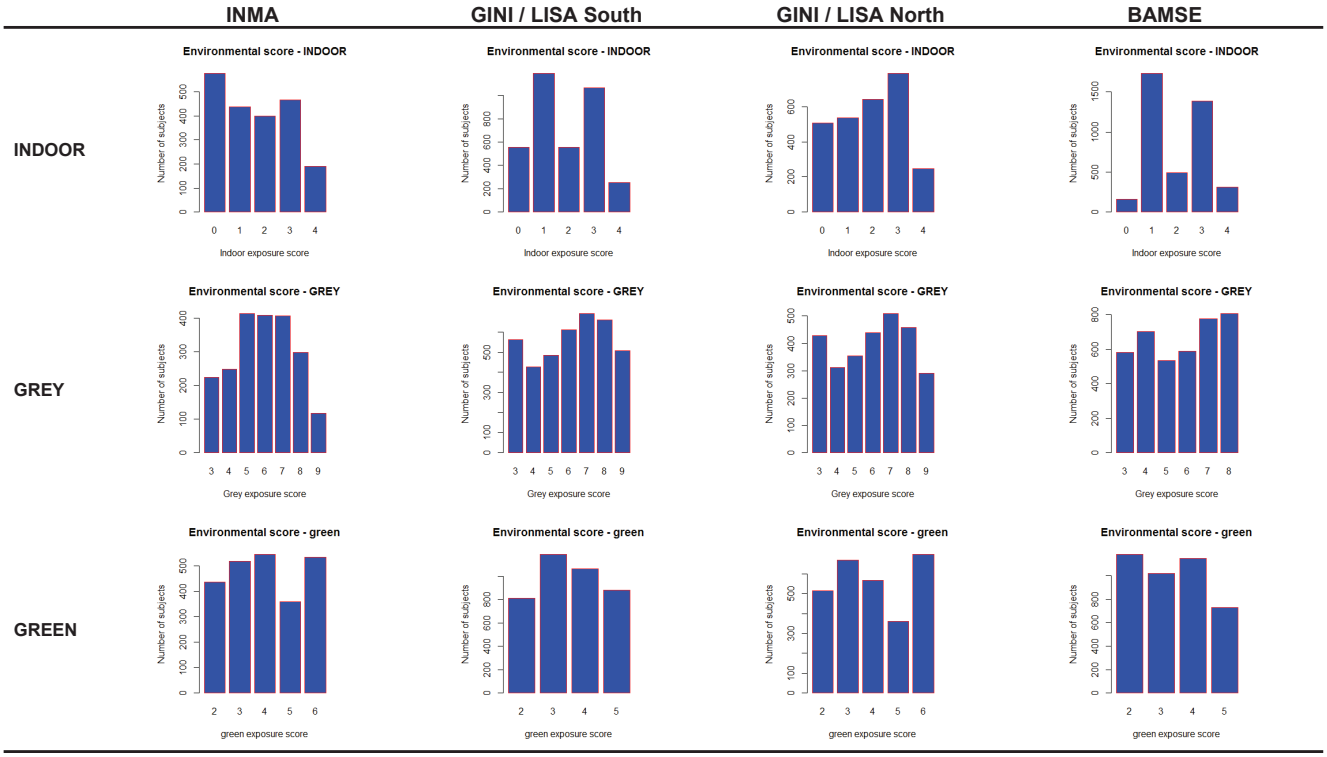
Supplementary Table 3: Cohort-specific health outcome assessment at different time points

INMA	
Wheezing 1st y	*Asturias (At 18 months): "How many wheezing episodes had your child, apart from cold, since the last 6 months?" (to have wheeze is defined by having 1 episode or more)* *Gipuzkoa (At 14 months): "How many wheezing episodes had your child, apart from cold?" (to have wheeze is defined by having 1 episode or more)* *Sabadell (At 14 months): "How many wheezing episodes had your child, apart from cold since the last 6 months?" (to have wheeze is defined by having 1 episode or more)* *Valencia (At 12 months): "How many wheezing episodes had your child, apart from cold in the last 12 months?" (to have wheeze is defined by having 1 episode or more)*
Bronchitis 1st y	*Asturias (At 18 months): "Has a doctor diagnosed your child with bronchitis since the last 6 months?"* *Gipuzkoa (At 14 months): "Has a doctor diagnosed your child with bronchitis since birth?"* *Sabadell (At 14 months): "Has a doctor diagnosed your child with bronchitis since the last 6 months?"* *Valencia (At 12 months): "Has a doctor diagnosed your child with bronchitis in the last 12 months?"*
Asthma 7 y	*Has your child ever been diagnosed by a doctor as having asthma?*
Allergic Rhinitis 7 y	*Has your child ever been diagnosed with having allergic rhinitis or hay fever?*
GINIplus	
Wheezing 1st y	*In the past 12 months, did your child have wheezing or whistling sounds in the chest while breathing? (yes/no)*
Bronchitis 1st y	*Doctor diagnosed bronchitis past 12 months*
Asthma 6 years	*Doctor diagnosed asthma past 12 months*
Allergic Rhinitis 6 y	*Doctor diagnosed allergic rhinitis or hay fever past 12 months*
IgE aero allergens 6y	*SX1 (cat dander, dog dander, dust mites, timothy, rye, Cladosporium herbarum, birch, mugwort): subjects with specific IgE values higher than 0.35 kU/l were regarded as sensitized (Pharmacia CAP System (Pharmacia Diagnostics, Freiburg, Germany)*
LISAplus	
Wheezing 1st y	*6 months and 1st year: In the past 6 months, did your child have wheezing or whistling sounds in the chest while breathing without having a cold? (yes/no)*

Bronchitis 1st y	*Doctor diagnosed bronchitis past 12 months*
Asthma 6 years	*Doctor diagnosed asthma past 12 months*
Allergic Rhinitis 6 y	*Doctor diagnosed allergic rhinitis or hay fever past 12 months*
IgE aero allergens 6y	*SX1 (cat dander, dog dander, dust mites, timothy, rye, Cladosporium herbarum, birch, mugwort): subjects with specific IgE values higher than 0.35 kU/l were regarded as sensitized (Pharmacia CAP System (Pharmacia Diagnostics, Freiburg, Germany)*

BAMSE

Wheezing 1st y	*Has your child ever had problems involving: Wheezy breathing*
Asthma 8 years	*Has your child been diagnosed with asthma by a doctor since age 4?*
Allergic Rhinitis 8 y	*Has your child been diagnosed with hay fever by a doctor since age 4?*
IgE aero allergens 8y	*Phadiatop® [a mix of common inhalant allergens: birch, timothy, mugwort, cat, dog, horse, mold (Cladosporium herbarum) and house dust mite (Dermatophagoides pteronyssinus)] (ImmunoCAP System, Phadia AB, Uppsala, Sweden). Cut off ≥0.35 kUA/l.*



Supplementary figure 1: Cohort-specific distribution of the Environmental scores

Supplementary Table 4: Exposure to environmental scores on later asthma and allergic rhinitis with and without IgE to aero-allergens (6-8y), stratified by cohort and total effect (Random effects model)*.

		Asthma 6-8 years + IgE	Asthma 6-8 years - IgE	Allergic Rhinitis 6-8 years + IgE	Allergic Rhinitis 6-8 years - IgE
Indoor Score	GINI/LISA South	6y: 0.84 (0.63-1.13)	6y: 1.20 (0.77-1.86)	6y: 0.77 (0.64-0.92)	6y: 0.88 (0.59-1.33)
	GINI/LISA North	6y: 0.83 (0.57-1.20)	6y: 0.83 (0.52-1.31)	6y: 0.92 (0.71-1.18)	6y: 0.90 (0.61-1.32)
	BAMSE	8y: 0.98 (0.80-1.21)	8y: 1.14 (0.88-1.46)	8y: 0.89 (0.74-1.06)	8y: 0.61 (0.35-1.07)
	Total	0.91 (0.78-1.07)	1.08 (0.89-1.32)	**0.85 (0.76-0.95)**	0.83 (0.64-1.06)
Grey Score	GINI/LISA South	6y: 0.89 (0.74-1.07)	6y: 0.86 (0.65-1.14)	6y: 0.95 (0.85-1.05)	6y: 0.89 (0.69-1.16)
	GINI/LISA North	6y: 1.06 (0.84-1.34)	6y: 1.10 (0.83-1.46)	8y: 1.04 (0.88-1.23)	6y: 0.95 (0.75-1.21)
	BAMSE	8y: 0.83 (0.73-0.95)	8y: 0.86 (0.73-1.01)	8y: 0.89 (0.79-0.99)	8y: 0.82 (0.59-1.13)
	Total	0.90 (0.79-1.03)	0.91 (0.79-1.05)	0.94 (0.87-1.02)	0.90 (0.77-1.05)
Green Score	GINI/LISA South	6y: 1.14 (0.81-1.60)	6y: 0.80 (0.48-1.33)	6y: 1.06 (0.86-1.29)	6y: 0.92 (0.58-1.48)
	GINI/LISA North	6y: 0.89 (0.65-1.21)	6y: 0.89 (0.61-1.29)	6y: 0.95 (0.77-1.19)	6y: 1.08 (0.79-1.49)
	BAMSE	8y: 1.32 (1.06-1.64)	8y: 1.27 (0.98-1.65)	8y: 1.13 (0.95-1.35)	8y: 1.46 (0.85-2.49)
	Total	1.12 (0.88-1.42)	1.02 (0.76-1.37)	1.06 (0.94-1.18)	1.10 (0.87-1.40)

*Adjusted for: sex, cohort, maternal allergy, maternal smoking during pregnancy, maternal education, breastfeeding, dampness at home 1st year, exposure to passive smoke 1st year.

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