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4 **1 Urban upbringing and childhood respiratory and allergic conditions:**
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6 **2 a multi-country holistic study.**
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117 **Abstract**

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

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

131 **Results:** A higher early exposure to the indoor environmental score increased the risk
132 for wheezing and bronchitis within the first year of life (combined adjusted odds ratio:
133 1.20 [95% confidence interval: 1.13-1.27] and 1.28 [1.18-1.39], respectively). In contrast,
134 there was an inverse association with allergic rhinitis between 6 and 8 years (0.85 [0.79-
135 0.92]). There were no statistically significant associations for the outdoor related
136 environmental scores in relation to any of the health outcomes tested. The factor analysis
137 conducted confirmed these trends.

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

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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), LISApplus (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), NO₂ (Nitrogen dioxide), FA (Factor Analysis),

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160 INTRODUCTION

161 The prevalence of asthma and allergic conditions is increasing worldwide (1) and has
162 coincided with the rapid and ongoing increase in the percentage of the population
163 residing in urban areas (2). The higher prevalence of asthma and allergic conditions in
164 urban areas compared to the rural areas suggests that urban-related environmental
165 factors may contribute to the pathogenesis of these conditions (3). Previous efforts to
166 evaluate such contributions have mainly focused on a single indoor or outdoor
167 environmental factor (while adjusting for other exposures). In general, there is a plethora
168 of evidence to suggest both positive and negative associations with various indoor and
169 outdoor factors and respiratory health outcomes. Some environmental factors are of
170 particular interest as they demonstrate strong associations with respiratory outcomes
171 (4). For instance, growing up on a farm and thereby having a higher exposure to farm
172 animals, animal feed or unprocessed cow's milk has been shown to protect children from
173 asthma, hay fever and allergic sensitization (5). These associations have been explained
174 by the 'hygiene hypothesis' (6); an early, more intense contact to microbial agents might
175 modulate and program the developing of an immune system towards a non-allergic
176 response (7,8). Much less is known regarding 'beneficial' exposure conditions in urban
177 areas. Nevertheless, previous literature in populations from affluent countries suggests
178 the existence of an inverse association between number of siblings and reported
179 prevalence of allergy-prone diseases, such as hay fever in later childhood due to
180 increased exposure to infections early in life as well as shedding and sharing microbial
181 exposures through more frequent contact (9,10). Further, a recent study among adults
182 observed that a higher proxy for microbial biodiversity in inner city environments,
183 represented by early childhood exposure to pets, day care, bedroom sharing and older
184 siblings, was related to less allergic sensitization (11). Moreover, early exposure to pets,
185 in particular dogs, has been repeatedly suggested to be associated with a reduced risk
186 of (non-atopic) asthma outcomes (12), although overall, associations are inconsistent
187 (13,14). In contrast, associations are rather consistent for exposure to moisture and

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188 mould damage at home in relation to increased risk for asthma and respiratory conditions
189 among children worldwide. Harmful effects of early secondhand tobacco smoke (SHS)
190 exposure in relation to these outcomes have also been documented among children
191 (15,16).

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

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

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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), LISApplus (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

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593 244 *home (excluding the study child)?” (=1 if ≥ 1 , =0 if =0), (3) “How many persons sleeping*
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595 245 *in one room together with the study child?” (=1 if ≥ 1 , =0 if =0), and (4) “How many people*
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597 246 *live permanently in the household together with the study child (excluding the study child*
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599 247 *for INMA (=1 if > 2 , =0 if ≤ 2), including the study child for GINIplus, LISApplus, and*
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601 248 *BAMSE)?” (=1 if > 3 , =0 if ≤ 3). The combined effect (sum of these scores) was examined*
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603 249 *together as the cumulative “indoor score” (ranged from 0 to 4).*

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607 251 OUTDOOR-GREEN and OUTDOOR-GREY environmental scores

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609 252 *Outdoor-green environmental score*

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611 253 We used (i) residential surrounding greenness and (ii) neighbourhood green land use to
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613 254 construct our outdoor-green environmental score. The assessment of residential
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615 255 surrounding greenness was based on the satellite-derived Normalized Difference
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617 256 Vegetation Index (NDVI). The NDVI is an indicator of greenness based on land surface
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619 257 reflectance of visible red and near-infrared parts of the spectrum (22). Its values range
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621 258 between -1 and 1 , with higher positive numbers indicating more greenness (i.e.
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623 259 photosynthetically-active vegetation). To characterise neighborhood green land use
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625 260 pattern, the CORINE land-cover classes were applied. The CORINE framework,
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627 261 developed by the European Environmental Agency, is a Europe-wide satellite-based
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629 262 inventory of land-cover categorized into 44 classes at a scale of 1:100000 (23) at
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631 263 different levels, last updated in 2011. To define the neighborhood green land use
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633 264 patterns (m^2), the surface area of Level 2 land cover (arable land, forests, heterogeneous
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635 265 agricultural land use types, open spaces with little or no vegetation, pastures, permanent
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637 266 crops, green urban area, sport and leisure facilities and shrub or herbaceous vegetation)
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639 267 within a 300 m buffer around the home address was summed.

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643 269 For each of the two aspects, a 3-level dummy variable (1 = low, 2 = medium and 3 =
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645 270 high) was created based on tertile values. For GINI/LISA South and BAMSE, the
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647 271 categorization of residential green land use patterns into tertiles was not applicable

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652 272 because the cut-offs were the same for the first 2 tertiles. Therefore, the median was
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654 273 used as the cut-off (1=lower residential green land use, 2=higher residential green land
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656 274 use). The "outdoor-green environmental score" was then abstracted by adding the
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658 275 scores for residential surrounding greenness and neighbourhood green land use
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660 276 (ranging from 2 to 5 for GINI/LISA South and BAMSE and 2 to 6 for INMA and GINI/LISA
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662 277 North).

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666 279 *Outdoor-grey environmental score*

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668 280 We applied (i) residential surrounding urban land use, (ii) NO₂ levels, and (iii) distance
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670 281 to major road to create outdoor-grey environmental score for each participant. To define
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672 282 residential surrounding urban land use patterns (m²), the surface area of Level 2
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674 283 CORINE land cover (includes industrial, commercial units, transport units, and mines)
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676 284 within a 300 m buffer around the home address was summed. Further, within all cohorts
677
678 285 we had information on exposure to NO₂ based on existing area-specific land use
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680 286 regression models and applied to the residence around birth. Finally, available
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682 287 harmonized data on distance to major road with constant traffic (in meters) was used
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684 288 (see **Supplementary Table 1**).

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688 290 As for the outdoor-green score, a 3-level dummy variable (1 = low, 2 = medium and 3 =
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690 291 high) was created based on tertiles of each exposure characteristic. For BAMSE, it was
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692 292 not possible to use tertiles due to the reasons already mentioned above. Thus, two
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694 293 categories were generated based on the median surface area (1=lower residential urban
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696 294 land use, 2=higher residential urban land use). Ultimately, the outdoor-grey
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698 295 environmental score was constructed adding the aforementioned three indicators, which
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700 296 ranged from 3 to 8 for BAMSE and 3 to 9 for the remaining cohorts.

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703 298 2) Data-driven approach (confirmatory analysis)

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711 299 The second data-driven approach (“confirmatory analysis”) was performed to evaluate
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713 300 the assessment of the environmental scores as well as their associations with the health
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715 301 outcomes. Specifically, the same environmental exposure data as used for building the
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717 302 environmental scores was applied in a factor analysis.
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721 304 According to the results of the cohort-specific FA, the three selected dimensions
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723 305 explained nearly two-third of the variation (see **Supplementary Table 2**). With respect
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725 306 to all participating birth cohorts, the first dimension was associated with residential
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727 307 surrounding greenness as well as air pollution from traffic (“Greenness/Air pollution”).
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729 308 The second dimension showed high loadings on number of people in the home as well
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731 309 as on whether there are (older) children which we defined as “Crowding”. This is
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733 310 comparable to the Indoor Environmental Score, however, it does not include microbial
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735 311 exposure associated with pets. Finally, the third dimension was in particular associated
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737 312 with exposure to pets. For the confirmatory regression analyses, only dimension 1
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739 313 (“Greenness/Air pollution”) and dimension 2 (“Crowding”) were considered as
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741 314 comparable to the subjectively built Environmental scores. We nonetheless performed
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743 315 regression analyses with the third dimension (“Pets”) as an exposure, but found no
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745 316 significant results with any of the health outcomes tested (data not shown).
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748 318 *Health outcome assessment*

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750 319 We focused on parental completed questionnaire information on (presumably infectious)
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752 320 respiratory outcomes including *wheezing* and *bronchitis* within the first year, as well as
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754 321 on current allergy-prone respiratory outcomes *asthma* and *allergic rhinitis / hay fever* in
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756 322 later childhood (INMA: 7y, GINI/LISA south and north: 6y, BAMSE: 8y). For all cohorts
757
758 323 except for INMA, there were further data available on atopic status (specific
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760 324 immunoglobulin E (IgE) > 0.35 kU/l) at 6 and 8 years, respectively. Detailed information
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762 325 of the health outcome assessment in the birth cohorts is provided in the **Supplementary**
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764 326 **Table 3**.

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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 LISApplus). 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.

827
828
829 355 All statistical analyses were performed using the statistical software R, version 3.4.0 (26)
830
831 356 (R Core Team (2015). R: A language and environment for statistical computing. R
832
833 357 Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>),
834
835 358 using FAmix within the “PCAmixdata” package for factor analysis (27).
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841 361 **RESULTS**

842 362 *Study population and environmental scores*

843 363 The study population and exposure characteristics are displayed in **Table 1**. The cohort-
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845 364 specific distribution of the environmental scores can be found in **Supplementary figure**
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847 365 **1**.
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852 367 *Main analysis: Associations between environmental scores and health outcomes*

853 368 Overall, as displayed in **Table 2**, a higher indoor environmental score, was found to
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855 369 increase the risk for wheezing and bronchitis outcomes within the first year of life in
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857 370 adjusted random-effects meta-analyses (aOR 1.20 [1.13-1.27] and 1.28 [1.18-1.39],
858
859 371 respectively). In contrast, we observed statistically significant inverse associations
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861 372 between a higher indoor environmental score with allergic rhinitis in later childhood (0.93
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863 373 [0.85-1.02] and 0.85 [0.79-0.92], respectively). For the remaining environmental scores,
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865 374 no statistically significant associations were obtained.
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870 376 There were no major differences in the results when the analyses were stratified by
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872 377 atopic status, except that there was a slightly more pronounced inverse effect between
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874 378 exposure to the indoor score and allergic rhinitis among atopic children (0.85 [0.76-0.95])
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876 379 compared to the non-atopic children (0.83 [0.64-1.06], **Supplementary Table 4**).
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878 380 Further, including “dampness” and “daycare before the second birthday” as additional
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880 381 sources of microbial exposure to the indoor score did not change the magnitude or
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882 382 direction of the effect estimates for any of the outcomes tested (data not shown).
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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

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

418
419 Studies have suggested that lifestyles associated with early exposures to farm and rural
420 environments may be associated with higher and diverse microbial exposures, and that
421 this might in turn lower the risk of allergic immune responses later in childhood and
422 adulthood (28,29). The indoor and outdoor related microbial profile in *urban*
423 environments might differ considerably from those in rural areas, in terms of levels,
424 composition, and diversity (30), and therefore might also have different effects on allergic
425 outcomes.

426
427 Lower prevalences of hay fever and allergic sensitization have also been consistently
428 observed with a higher number of (older) siblings in urban areas (9,10). Family size or
429 more frequent human contact in general is suggested to be a source of higher microbial
430 and viral exposure through shedding and sharing (6,31). According to the “hygiene
431 hypothesis” (6), this might have the potential to attenuate the harmful effects of increased
432 hygienic conditions and lower xenogeneic pressure associated with a “Westernized” life
433 style on the maturing immune system, resulting in increased risks for allergy prone
434 diseases in urban environments. In fact, although we here consistently observed that a
435 higher suggested microbial and viral load indoors (through occupants) around birth was
436 strongly associated with a higher risk of infections during the first year of life, this
437 association was reversed for asthma and allergic rhinitis later in childhood. Further, for
438 two out of four participating birth cohorts, sizeable inverse associations with allergic

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1006 439 rhinitis were also found when we additionally included daycare attendance before the
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1008 440 second birthday in the calculation of the indoor score. A recent urban birth cohort study
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1010 441 in the U.S. observed a bi-directional relationship between cumulative early day care
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1012 442 attendance with asthma, pointing out a reduced risk for asthma with increased duration
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1014 443 of daycare attendance (> 1800 hours) (32). Further, previous studies looking at the health
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1016 444 effects of early higher exposure to microbial components in *urban* settled house dust
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1018 445 (most prominently, floor and mattress dust) are also partly in line with our findings for
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1020 446 asthma and allergic rhinitis.

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1024 448 According to the available literature, higher and more diverse microbial loads indoors
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1026 449 have been associated with lower risks for allergic outcomes in a few small-scale studies
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1028 450 (33–35). Lastly, the combination of a large family size and exposure to farming was
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1030 451 especially associated with a remarkable decrease in hay fever (36). However, it was not
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1032 452 possible to disentangle the effects of both protective factors, suggesting two different
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1034 453 biological mechanisms and pointing out the magnitude of both environmental
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1036 454 determinants in relation to allergy prone diseases.

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1039 456 Our results indicate an important signal of *human* derived and transferred microbial and
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1041 457 viral exposure in homes in relation to early respiratory infections and childhood allergic
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1043 458 rhinitis. These effects appeared more important than those related to outdoor
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1045 459 characteristics. Though “crowding” has been also suggested to be a risk factor for
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1047 460 hospitalization in childhood and viral infections are the major cause of acute wheezing
1048
1049 461 exacerbation in early life (37), viral respiratory infections are very common. For most
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1051 462 children, no negative impact in later life is expected – unless they are impaired by host
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1053 463 factors or deficiencies in the innate immune response to these agents (38). We also
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1055 464 included “exposure to pets” in the indoor environmental score, however, “crowding”, as
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1057 465 identified by the factor analysis, was exclusively based on person associated factors.

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

480
481 It is assumed that indoor microbial communities are part of the closer neighborhood and
482 built environment (42). Therefore, the simultaneous exposure to indoor and outdoor
483 environmental exposures might play even a more important role for metropolitan areas
484 compared to rural areas due to a presumably more heterogeneous exposure profile of
485 coincident hazardous and protective factors (18,43). While there remained a consistent
486 strong inverse association between exposure to suggested higher microbial load
487 indoors, as determined by the indoor score and “crowding”, on later asthma and allergic
488 rhinitis outcomes in all sensitivity analyses, the associations were less coherent for the
489 remaining environmental exposure constructs.

490
491 In general, compared to natural surroundings, artificial green urban areas can also be
492 potential sources of harmful allergen exposure (44,45). Fundamentally, it is likely that
493 associations with respiratory and allergic health will depend on the allergenicity of the
494 respective green exposure surrounding the participants (19,46,47). Moreover, the

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1124 495 contextual factors describing the outdoor environment are highly area-specific and a
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1126 496 more detailed exposure characterization would be desirable. Unfortunately, this was not
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1128 497 possible for the current publication as the aim was to capture a wide geographical region
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1130 498 and the exposure characteristics were restricted to those commonly available.
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1134 500 Future studies which consider region-specific outdoor characteristics at a finer scale are
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1136 501 therefore recommended (48). In summary, the results of our study underline the
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1138 502 importance of early exposure to *indoor* related characteristics in comparison to outdoor
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1140 503 related characteristics with respect to respiratory and allergic health outcomes in
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1142 504 urbanized residential surroundings.
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1146 506 A key strength of this study is its comprehensive approach, integrating indoor as well as
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1148 507 outdoor environmental exposures in relation to respiratory and allergic health outcomes.
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1150 508 Other advantages were the large sample size of the birth cohorts, the harmonized
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1152 509 exposure and health outcome assessments, information on several important
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1154 510 confounders and the inclusion of regions across the north, center, and south of Europe.
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1158 512 Limitations of the study include the fact that we could not consider further potentially
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1160 513 relevant (built) environment factors such as the school environment, which may act as
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1162 514 additional source of regular microbial exposure. In addition, although we had in a large
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1164 515 part harmonized exposure and health outcome information across all birth cohorts, we
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1166 516 only included exposures which were available and identically assessed in all study
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1168 517 populations which might have led to an unknown amount of information loss.
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1170 518 Unfortunately, an identical health outcome assessment was not possible due to regional
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1172 519 differences within the populations. In this context, we also did not have data on the *actual*
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1174 520 microbial exposure, e.g. as determined in dust samples, associated with the respective
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1176 521 environmental exposure domains. For the indoor environmental domain in the main
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1178 522 analyses, we only focused on suggested higher microbial load exposure and excluded

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1183 523 potential harmful exposures such as dampness and passive smoke exposure.
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1185 524 Nevertheless, all statistical models were adjusted for dampness as well as passive and
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1187 525 *in utero* tobacco smoke exposure. Apart from that, including more sources related to
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1189 526 hazardous exposure characteristics in the FA did neither change the “dimensions”
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1191 527 assignment, nor result in a coherent third exposure dimension. Lastly, although infections
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1193 528 are crucial in the pathogenesis of allergic diseases and a more accurate information by
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1195 529 serology or culture would be desirable, we have to rely on parental reported diseases.
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1197 530

1198 531 **Conclusion**

1199 532 Our study indicates that, in particular early exposure to a suggested higher microbial load
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1201 533 indoors is associated with an increased risk of presumably infection-prone wheezing and
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1203 534 bronchitis in early childhood but with a decreased risk for asthma and allergic rhinitis
1204
1205 535 later in childhood. There were no coherent findings for exposure to outdoor related
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1207 536 environmental factors, which highlights the importance of indoor related factors in early
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1209 537 life over outdoor related sources in adjusted analyses. The assumed biological
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1211 538 mechanism might be an early and more intense encounter with viruses and higher
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1213 539 microbial load associated with greater family size. If specific exposure can be identified,
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1215 540 e.g. obtained through dust samples in homes with greater family size or daycare centers,
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1217 541 this might serve substantial preventive capability.
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1222 544 **Acknowledgement**

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1224 545 We thank the participating children, their families and the fieldworkers of the included
1225
1226 546 birth cohorts BAMSE, GINplus, INMA, and LISApplus.
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1230 548 **Contributions**

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1232 549 Conception and design: CT, PD, JS, XB, JMA

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1234 550 Analysis and interpretation: CT, XB, PD, JS
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1242 551 Critical revising the manuscript and allocation of data: CT, JS, LC, EF, AB, OG, EM,
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1244 552 DB, JH, SK, IM, MS, DS, LC, ME, AFS, AF, JI, AL, AT
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1248 554 **Conflict(s) of Interest**
1249
1250 555 None.
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1254 557 **Ethics committee approval**
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1256 558 For the included studies, approval by the local ethics committees and written consent
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1258 559 from participants' families were obtained.
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561 **REFERENCES**

- 562 1. Asher MI. Urbanisation , asthma and allergies. *Thorax*. 2011;66(12):1025–6.
- 563 2. Gern J. The Urban Environment and Childhood Asthma Study. *J Allergy Clin Immunol*.
- 564 2010;125(3):545–9.
- 565 3. Brasier AR. Heterogeneity in Asthma. Brasier AR, editor. Texas: Springer; 2014.
- 566 4. Heinrich J. Influence of indoor factors in dwellings on the development of childhood
- 567 asthma. *Int J Hyg Env Heal* [Internet]. 2010/09/21. 214(1):1–25. Available from:
- 568 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20851050)
- 569 [ation&list_uids=20851050](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20851050)
- 570 5. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev*
- 571 *Immunol* [Internet]. 2010/11/10. 2010;10(12):861–8. Available from:
- 572 <http://dx.doi.org/10.1038/nri2871>
- 573 6. Strachan DP. Hay fever, hygiene, and household size. *BMJ* [Internet]. 1989/11/18.
- 574 1989;299(6710):1259–60. Available from:
- 575 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2513902)
- 576 [ation&list_uids=2513902](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2513902)
- 577 7. Braun-Fahrlander C, Lauener R. Farming and protective agents against allergy and
- 578 asthma. *ClinExpAllergy*. 2003;33(4):409–11.
- 579 8. Lauener RP, Birchler T, Adamski J, Braun-Fahrlander C, Bufe A, Herz U, et al. Expression
- 580 of CD14 and Toll-like receptor 2 in farmers' and non-farmers' children. *Lancet*.
- 581 2002;360(9331):465–6.
- 582 9. D. P. Strachan, D.P., A€it-Khaled, N., Foliaki, S, Mallol, J., Odhiambo, J., Pearce, N.,
- 583 Williams HC and the IPTS group. Siblings, asthma, rhinoconjunctivitis and eczema: a
- 584 worldwide perspective from the International Study of Asthma and Allergies in
- 585 Childhood. *Clin Exp Allergy*. 2014;45:126–36.
- 586 10. Kramer U, Schmitz R, Ring J, Behrendt H. What can reunification of East and West

1358
1359
1360 587 Germany tell us about the cause of the allergy epidemic? Clin Exp Allergy.
1361
1362 588 2015;45(1):94–107.
1363
1364 589 11. B Campbell, B, Raheison, C, Lodge, C, Lowe, A, Gislason, T, Heinrich, J, Sunyer, J, Gomez
1365
1366 590 Real, F, Norbäck, D, Matheson, M, Wjst, M, Dratva, J, de Marco, R, Jarvis, D, Schlünssen,
1367
1368 591 V, Janson, C, Leynaert, B, Svanes, C, Dharmage S. The effects of growing up on a farm
1369
1370 592 on adult lung function and allergic phenotypes: an international population-based
1371
1372 593 study. Thorac Cardiovasc Surg. 2016;
1373
1374 594 12. Collin, S M, Granell, R, Westgarth, C, Murray J, Paul E, Sterne, JA, Henderson J. Pet
1375
1376 595 ownership is associated with increased risk of non-atopic asthma and reduced risk of
1377
1378 596 atopy in childhood: findings from a UK birth cohort. Clin Exp Allergy. 2015;45(1):200–
1379
1380 597 10.
1381
1382 598 13. Chen CM, Tischer C, Schnappinger M, Heinrich J. The role of cats and dogs in asthma
1383
1384 599 and allergy--a systematic review. Int J Hyg Env Heal [Internet]. 2010/01/08.
1385
1386 600 2010;213(1):1–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20053584>
1387
1388 601 14. Lodrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, et al. Does
1389
1390 602 pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of
1391
1392 603 individual participant data from 11 European birth cohorts. PLoS One [Internet].
1393
1394 604 2012/09/07. 2012;7(8):e43214. Available from:
1395
1396 605 <http://www.ncbi.nlm.nih.gov/pubmed/22952649>
1397
1398 606 15. Thacher JD, Gruzieva O, Pershagen G, Neuman A, Hage M Van, Wickman M, et al.
1399
1400 607 Parental smoking and development of allergic sensitization from birth to adolescence.
1401
1402 608 Allergy. 2016;71:239–48.
1403
1404 609 16. Mendell, M.J., Kumagai K. Observation-based metrics for residential dampness and
1405
1406 610 mold with dose-response relationships to health: A review. 2016;(July):1–12.
1407
1408 611 17. Haahtela T, Holgate S, Pawankar R, Akdis CA, Benjaponpitak S, Caraballo L, et al. The
1409
1410 612 biodiversity hypothesis and allergic disease: world allergy organization position
1411
1412
1413
1414
1415
1416

1417
1418
1419 613 statement. World Allergy Organ J [Internet]. 2013;6(1):3. Available from:
1420
1421 614 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23663440)
1422
1423 615 [ation&list_uids=23663440](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23663440)
1424
1425 616 18. Pilat MA, McFarland A, Snelgrove A, Collins K, Waliczek TM, Zajicek J. The effect of tree
1426
1427 617 cover and vegetation on incidence of childhood asthma in metropolitan statistical areas
1428
1429 618 of Texas. Horttechnology. 2012;22(5):631-7.
1430
1431 619 19. Ruokolainen L, von Hertzen L, Fyhrquist N, Laatikainen T, Lehtomäki J, Auvinen P, et al.
1432
1433 620 Green areas around homes reduce atopic sensitization in children. Allergy [Internet].
1434
1435 621 2015;70(2):195-202. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25388016>
1436
1437 622 20. Gehring U, Wijga AH, Hoek G, Bellander T, Berdel D, Brüske I, et al. Exposure to air
1438
1439 623 pollution and development of asthma and rhinoconjunctivitis throughout childhood
1440
1441 624 and adolescence : a population-based birth cohort study. Lancet Respir. 2015;933-42.
1442
1443 625 21. Molter A, Simpson A, Berdel D, Brunekreef B, Custovic A, Cyrus J, et al. A multicentre
1444
1445 626 study of air pollution exposure and childhood asthma prevalence: the ESCAPE project.
1446
1447 627 Eur Respir J [Internet]. 2014/10/18. 2014; Available from:
1448
1449 628 <http://www.ncbi.nlm.nih.gov/pubmed/25323237>
1450
1451 629 22. Weier J HD. Measuring Vegetation (NDVI & EVI). [Internet]. 2011. Available from:
1452
1453 630 <http://earthobservatory.nasa.gov/Features/MeasuringVegetation/>
1454
1455 631 23. Eea. CORINE land cover - contents. Methodology [Internet]. 1994;1-163. Available
1456
1457 632 from: <http://www.eea.europa.eu/publications/COR0-landcover/page001.html>
1458
1459 633 24. Brian S. Everitt and Torsten Hothorn. Logistic Regression and Generalised Linear
1460
1461 634 Models: Blood Screening, Women's Role in Society, and Colonic Polyps. 2015.
1462
1463 635 25. R, DerSimonian LN. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.
1464
1465 636 26. R Core Team. Statistical Analysis with R [Internet]. Vienna: The R Foundation for
1466
1467 637 Statistical Computing; 2015. Available from: <https://www.r-project.org/>
1468
1469 638 27. Marie Chavent, Vanessa Kuentz, Amaury Labenne BL and JS. PCAmixdata: Multivariate
1470
1471
1472
1473
1474
1475

1476
1477
1478 639 Analysis of Mixed Data. [Internet]. 2014 [cited 2017 Jun 18]. Available from:
1479
1480 640 <https://cran.r-project.org/package=PCAmixdata>
1481
1482 641 28. von Mutius E. The microbial environment and its influence on asthma prevention in
1483
1484 642 early life. *J Allergy Clin Immunol* [Internet]. 2015;137(3):680–9. Available from:
1485
1486 643 <http://dx.doi.org/10.1016/j.jaci.2015.12.1301>
1487
1488 644 29. Ege MJ, Mayer M, Normand A-C, Genuneit J, Cookson WO, Braun-Fahrländer C, et
1489
1490 645 al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*
1491
1492 646 [Internet]. 2011/02/25. 2011;364(8):701–9. Available from:
1493
1494 647 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21345099)
1495
1496 648 [ation&list_uids=21345099](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21345099)
1497
1498 649 30. Pakarinen J, Hyvärinen A, Salkinoja-Salonen M, Laitinen S, Nevalainen A, Mäkelä MJ, et
1500
1501 650 al. Predominance of Gram-positive bacteria in house dust in the low-allergy risk Russian
1502
1503 651 Karelia. *Environ Microbiol*. 2008;10(12):3317–25.
1504
1505 652 31. von Mutius E. Allergies, infections and the hygiene hypothesis--the epidemiological
1506
1507 653 evidence. *Immunobiology* [Internet]. 2007/06/05. 2007;212(6):433–9. Available from:
1508
1509 654 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17544828)
1510
1511 655 [ation&list_uids=17544828](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17544828)
1512
1513 656 32. Cheng G, Smith AM, Levin L, Epstein T, Ryan PH, Lemasters GK, et al. Duration of day
1514
1515 657 care attendance during infancy predicts asthma at the age of seven : the Cincinnati
1516
1517 658 Childhood Allergy and Air Pollution Study Experimental Allergy. 2014;1274–81.
1518
1519 659 33. Dannemiller KC, Mendell MJ, Macher JM, Kumagai K, Bradman a., Holland N, et al.
1520
1521 660 Next-generation DNA sequencing reveals that low fungal diversity in house dust is
1522
1523 661 associated with childhood asthma development. *Indoor Air* [Internet]. 2014;24(3):236–
1524
1525 662 47. Available from:
1526
1527 663 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24883433)
1528
1529 664 [ation&list_uids=24883433](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24883433)
1530
1531
1532
1533
1534

1535
1536
1537 665 34. Tischer C, Weigl F, Probst AJ, Standl M, Heinrich J, Pritsch K. Urban dust microbiome:
1538
1539 666 Impact on later atopy and wheezing. *Environ Health Perspect*. 2016;124(12):1919–23.
1540
1541 667 35. Lynch S V, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of
1542
1543 668 early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban
1544
1545 669 children. *J Allergy Clin Immunol* [Internet]. 2014/06/09. 2014;134(3):593–601 e12.
1546
1547 670 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24908147>
1548
1549 671 36. Genuneit J, Strachan DP, Bu G, Weber J, Loss G, Boznanski A, et al. The combined
1550
1551 672 effects of family size and farm exposure on childhood hay fever and atopy.
1552
1553 673 2013;24(4):293–8.
1554
1555 674 37. Colosia AD, Masaquel A, Hall CB, Barrett AM, Mahadevia PJ, Yogev R. Residential
1556
1557 675 crowding and severe respiratory syncytial virus disease among infants and young
1558
1559 676 children: A systematic literature review. *BMC Infect Dis* [Internet]. 2012;12(1):95.
1560
1561 677 Available from: [http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-](http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-12-95)
1562
1563 678 12-95
1564
1565 679 38. Von Mutius E. Epidemiology of Allergic Diseases. In: Leung Sampsom, H.A., Geha, R.,
1566
1567 680 Szeffler, S.J. DY, editor. *Pediatric Allergy: Principles and Practice*. Mosby; 2010.
1568
1569 681 39. Adams RI, Miletto M, Taylor JW, Bruns TD. Dispersal in microbes: fungi in indoor air are
1570
1571 682 dominated by outdoor air and show dispersal limitation at short distances. *ISME J*
1572
1573 683 [Internet]. 2013/06/26. 2013;7(7):1460. Available from:
1574
1575 684 <http://www.ncbi.nlm.nih.gov/pubmed/23797294>
1576
1577 685 40. Adams RI, Miletto M, Lindow SE, Taylor JW, Bruns TD. Airborne bacterial communities
1578
1579 686 in residences: similarities and differences with fungi. *PLoS One* [Internet].
1580
1581 687 2014;9(3):e91283. Available from:
1582
1583 688 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24603548)
1584
1585 689 [ation&list_uids=24603548](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24603548)
1586
1587 690 41. Barberán A, Dunn RR, Reich BJ, Pacifici K, Laber EB, Menninger HL, et al. The ecology of
1588
1589
1590
1591
1592
1593

1594
1595
1596 691 microscopic life in household dust. Proc R Soc B Biol Sci [Internet].
1597
1598 692 2015;282(1814):20151139. Available from:
1599
1600 693 <http://rspb.royalsocietypublishing.org/content/282/1814/20151139>
1601
1602 694 42. Weikl F, Tischer C, Probst AJ, Heinrich J, Markevych I, Jochner S, et al. Fungal and
1603
1604 Bacterial Communities in Indoor Dust Follow Different Environmental Determinants.
1605 695
1606 696 2016;1-15.
1607
1608 697 43. Casas L, Tischer C, Täubel M. Pediatric Asthma and the Indoor Microbial Environment.
1609
1610 Curr Environ Heal Reports [Internet]. 2016; Available from:
1611 698
1612 699 <http://link.springer.com/10.1007/s40572-016-0095-y>
1613
1614 700 44. Lovasi GS, O'Neil-Dunne JP, Lu JW, Sheehan D, Perzanowski MS, Macfaden SW, et al.
1615
1616 Urban tree canopy and asthma, wheeze, rhinitis, and allergic sensitization to tree pollen
1617 701
1618 in a New York City birth cohort. Environ Health Perspect [Internet]. 121(4):494-500.
1619 702
1620 Available from:
1621 703
1622 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Cit](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23322788)
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1625 705
1626 706 45. DellaValle CT, Triche EW, Leaderer BP, Bell ML. Effects of ambient pollen concentrations
1627
1628 on frequency and severity of asthma symptoms among asthmatic children.
1629 707
1630 Epidemiology [Internet]. 2012;23(1):55-63. Available from:
1631 708
1632 [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3246281&tool=pmcentrez](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3246281&tool=pmcentrez&rendertype=abstract)
1633 709
1634 [&rendertype=abstract](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3246281&tool=pmcentrez&rendertype=abstract)
1635 710
1636 711 46. Cariñanos P C-PM. Urban green zones and related pollen allergy: a review. Some
1637
1638 guidelines for designing spaces with low allergy impact. Landsc Urban Plan.
1639 712
1640 2011;101:205-14.
1641 713
1642 714 47. Fuertes E, Markevych I, Bowatte G, Gruzieva O, Gehring U, Becker A, et al. Residential
1643
1644 greenness is differentially associated with childhood allergic rhinitis and aeroallergen
1645 715
1646 sensitization in seven birth cohorts. Allergy [Internet]. 2016; Available from:
1647 716
1648
1649
1650
1651
1652

1653
1654
1655 717 <http://www.ncbi.nlm.nih.gov/pubmed/27087129>
1656
1657 718 48. Tischer, C; Gascon, M, Fernandez-Somoano, A; Tardon, A; Lertxundi Materola, A;
1658
1659 719 Ibarlueza, J; Ferrero, A; Estarlich, M; Cirach, M; Vrijheid, M; Fuertes, E; Dalmau-Bueno,
1660
1661 720 A; Nieuwenhuijsen, M; Anto, JM; Sunyer, J; Dadvand P. In Press: Urban green and grey
1662
1663 721 space in relation to respiratory health in children. ERJ. 2017;
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Table 1: Study population characteristics, exposure and health outcome information by birth cohort

cohort	INMA (N=2472)	GINI/LISA South (N=4413)	GINI/LISA North (N=3390)	BAMSE (N=4089)
HEALTH OUTCOMES				
Wheezing 1 st year	36%	15%	17%	15%
Bronchitis 1 st 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 1 st year	7%	5%	3%	10%
Asthma/no wheeze 1 st year	3%	2%	2%	4%
Asthma/bronchitis 1 st year	7%	4%	4%	7%
Asthma/no bronchitis 1 st 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 1 st year	4%	7%	7%	6%
Allergic rhinitis /no wheeze 1 st year	3%	5%	3%	5%
Allergic rhinitis /bronchitis 1 st year	5%	6%	7%	5%
Allergic rhinitis /no bronchitis 1 st 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 2 nd birthday	35%	-	-	72%
OUTDOOR grey and green (median)				
NDVI 100m buffer	0.25	0.30	0.30	0.22
Green index 300m buffer (m ²)	69330	3665	84530	0
Grey index 300m buffer (m ²)	193000	278800	198000	282600
NO ₂ (µg/m ³)	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 1 st year	10%	7%	4%	24%
Passive smoke 1 st year	47%	16%	30%	19%
Cohort	Asturias: 20% Gipuzkoa: 25% Sabadell: 31% Valencia: 24%	GINI: 67% LISA: 33%	GINI: 90% LISA: 10%	-

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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.

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723 **Table 3:** Exposure to environmental dimensions ("Outdoor exposure" and "Crowding") as identified by factor analysis and health outcomes,
724 stratified by cohort and total effect (Random effects model)*.
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		Wheezing 1st year	Bronchitis 1st year	Asthma 6-8 years	Allergic Rhinitis 6-8 years
DIM 1 „Outdoor exposure“	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)
	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 „Crowding“	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)
	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)

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

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Supplementary Data

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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

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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 LISApplus 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.

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

INMA	
Indoor	<ol style="list-style-type: none"> 1st year: <i>Do you or did you have animals at home since the birth of the child? (yes/no)</i> 1st year: <i>The child sleeps currently: alone / together with other persons</i> 3rd trimester: <i>Are there children younger than 12 year living in your home? (yes/no)</i> 1st year: <i>How many people live together with your child? (numeric)</i> 1st year: <i>Is your child visiting daycare? (no, yes-some hours, yes=full time)</i> 3rd trimester: <i>In your home, are there any signs of dampness? (combined: yes/no living-room / bedroom)</i>
Outdoor-green	<ol style="list-style-type: none"> Residential surrounding greenness (NDVI) 100m buffer: <i>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).</i> Green Index 300m buffer around the residential address
Outdoor-grey	<ol style="list-style-type: none"> Grey Index 300m buffer around the residential address (numeric) NO₂ exposure around birth (numeric) <i>Existing area-specific land use regression (LUR) models, applied to the residence during the first year of life in INMA (10).</i> Distance to nearest major road with permanent traffic (numeric)
GINIplus	
Indoor	<ol style="list-style-type: none"> 1st year: <i>Do you currently have pets in the home (first 4 months since birth)? (yes/no)</i> 1st year: <i>In the first 4 months since birth, how many persons slept together in a room with the child? (numeric)</i> 1st year: <i>How many persons belong to your household? (numeric), including the study child</i> 1st year: <i>How many persons (children) belong to your household? (numeric), including the study child</i> 1st year: <i>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)</i> 1st year: <i>Would you consider your flat as damp? (yes/no)</i>
Outdoor-green	<ol style="list-style-type: none"> Residential surrounding greenness (NDVI) 100m buffer: <i>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).</i> Green Index 300m buffer around the residential address
Outdoor-grey	<ol style="list-style-type: none"> Grey Index 300m buffer around the residential address (numeric)

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2. NO₂ 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)

LISApus

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| Indoor | <ol style="list-style-type: none"> 1. 3 months: <i>Do you currently have pets at home? (yes/no)</i> 2. 3 months: <i>In the first 3 months since birth, how many persons slept together in a room with the child? (numeric)</i> 3. 3 months: <i>How many persons belong to the household (including the study child)? (numeric)</i> 4. 3 months: <i>Number of children in the household (including the study child) (numeric)</i> 5. 3 months: <i>Would you consider your flat as damp? (yes/no)</i> |
| Outdoor-green | <ol style="list-style-type: none"> 1. Residential surrounding greenness (NDVI) 100m buffer
 <i>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 LISApus 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).</i> |
| Outdoor-grey | <ol style="list-style-type: none"> 2. Green Index 300m buffer around the residential address 1. Grey Index 300m buffer around the residential address (numeric) 2. NO₂ exposure at birth (numeric)
 <i>Existing area-specific land use regression (LUR) models, applied to the residence at the time of birth (12).</i> 3. Distance to nearest major road with permanent traffic (numeric) |

BAMSE

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| Indoor | <ol style="list-style-type: none"> 1. Birth: <i>Are there pets in the home? (yes/no)</i> 2. Birth: <i>How many people does the child share a bedroom with? (numeric)</i> 3. Birth: <i>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</i> 4. Birth: <i>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</i> 5. 2nd year: <i>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)</i> 6. Birth: <i>Is there, or has there ever been, any type of moisture damage (spots and the like) in the home? (yes/no)</i> |
| Outdoor-green | <ol style="list-style-type: none"> 1. Residential surrounding greenness (NDVI) 100m buffer
 <i>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.</i> |

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Outdoor-grey

2. Green Index 300m buffer around the residential address

1. Grey Index 300m buffer around the residential address (numeric)

2. NO₂ 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)

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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).

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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

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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

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

INMA	
Wheezing 1st y	<i>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)</i> <i>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)</i> <i>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)</i> <i>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)</i>
Bronchitis 1st y	<i>Asturias (At 18 months): "Has a doctor diagnosed your child with bronchitis since the last 6 months?"</i> <i>Gipuzkoa (At 14 months): "Has a doctor diagnosed your child with bronchitis since birth?"</i> <i>Sabadell (At 14 months): "Has a doctor diagnosed your child with bronchitis since the last 6 months?"</i> <i>Valencia (At 12 months): "Has a doctor diagnosed your child with bronchitis in the last 12 months?"</i>
Asthma 7 y	<i>Has your child ever been diagnosed by a doctor as having asthma?</i>
Allergic Rhinitis 7 y	<i>Has your child ever been diagnosed with having allergic rhinitis or hay fever?</i>
GINIplus	
Wheezing 1st y	<i>In the past 12 months, did your child have wheezing or whistling sounds in the chest while breathing? (yes/no)</i>
Bronchitis 1st y	<i>Doctor diagnosed bronchitis past 12 months</i>
Asthma 6 years	<i>Doctor diagnosed asthma past 12 months</i>
Allergic Rhinitis 6 y	<i>Doctor diagnosed allergic rhinitis or hay fever past 12 months</i>
IgE aero allergens 6y	<i>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))</i>
LISAplus	
Wheezing 1st y	<i>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)</i>

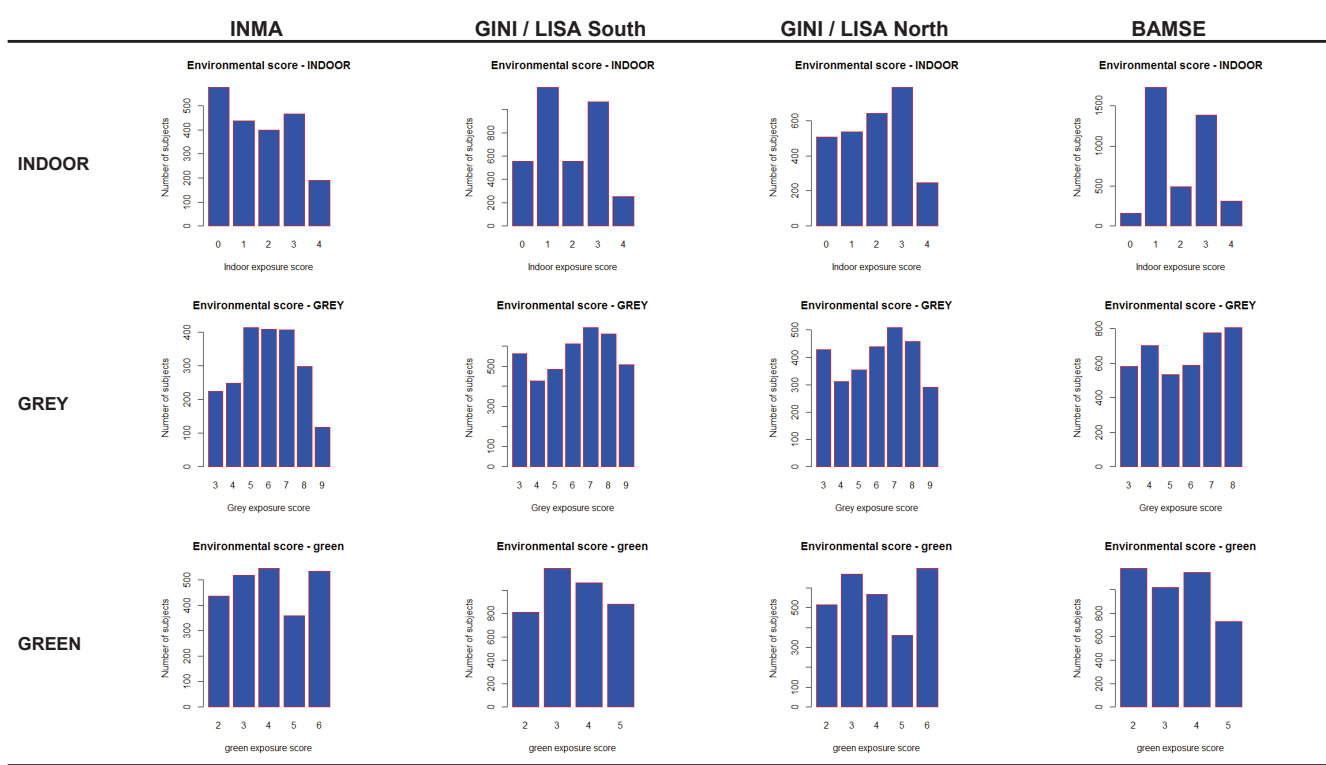
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Bronchitis 1st y *Doctor diagnosed bronchitis past 12 months*
Asthma 6 years *Doctor diagnosed asthma past 12 months*
Allergic Rhinitis 6 y *Doctor diagnosed allergic rhinitis or hay fever past 12 months*
IgE aero allergens 6y *SX1 (cat dander, dog 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))*

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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.*

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

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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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729 **References – SUPPLEMENTARY MATERIAL**
730

731 1. Guxens M, Ballester F, Espada M, Fernandez MF, Grimalt JO, Ibarluzea J, et al. Cohort Profile: The INMA--Infancia y Medio Ambiente--(Environment
732 and Childhood) Project. *Int J Epidemiol* [Internet]. 2011/04/08. 2012;41(4):930–40. Available from:
733 <http://www.ije.oxfordjournals.org/cgi/doi/10.1093/ije/dyr054>

734 2. von Berg, A., Krämer U., Link, E., Bollrath, C., Heinrich, J., Brockow, I., Koletzko, S., Grübl, A., Filipiak-Pittroff, B., Wichmann, H.-E., Bauer, C.-P.,
735 Reinhardt, D., Berdel DA the Gini study group. Impact of early feeding on childhood eczema: development after nutritional intervention compared
736 with the natural course – the GINIplus study up to the age of 6 years. *Clin Exp Allergy*. 2010;

737 3. Heinrich J, Bolte G, Hölscher B, Douwes J, Lehmann I, Fahlbusch B, et al. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E
738 in cord blood of neonates. *Eur Respir J Off J Eur Soc Clin Respir Physiol* [Internet]. 2002/10/03. 2002;20(3):617–23. Available from:
739 <http://www.ncbi.nlm.nih.gov/pubmed/12358337>

740 4. Zutavern A, von Klot S, Gehring U, Krauss-Etschmann S, Heinrich J. Pre-natal and post-natal exposure to respiratory infection and atopic diseases
741 development: a historical cohort study. *Respir Res* [Internet]. 2006/05/25. 2006;7:81. Available from:
742 <http://www.ncbi.nlm.nih.gov/pubmed/16719901>

743 5. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy
744 Immunol* [Internet]. 2003/04/12. 2002;13 Suppl 1:11–3. Available from:
745 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12688617

746 6. Dadvand P, Sunyer J, Basagaña X, Ballester F, Lertxundi A, Fernández-Somoano A, et al. Surrounding Greenness and Pregnancy Outcomes in Four
747 Spanish Birth Cohorts. *Environ Health Perspect* [Internet]. 2012;120(10):1481–7. Available from: <http://ehp.niehs.nih.gov/1205244>

748 7. Dadvand P, de Nazelle A, Figueras F, Basagaña X, Su J, Amoly E, et al. Green space, health inequality and pregnancy. *Environ Int* [Internet].
749 2011/08/10. 2012;40:110–5. Available from: <http://dx.doi.org/10.1016/j.envint.2011.07.004>

750 8. Dadvand P, de Nazelle A, Figueras F, Basagana X, Su J, Amoly E, et al. Green space, health inequality and pregnancy. *Env Int* [Internet]. 2011/08/10.
751 2012;40:110–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21824657>

752 9. Donovan GH, Michael YL, Butry DT, Sullivan AD, Chase JM. Urban trees and the risk of poor birth outcomes. *Heal Place* [Internet]. 2011;17(1):390–3.

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753 Available from: <http://dx.doi.org/10.1016/j.healthplace.2010.11.004>

754 10. Estarlich M, Ballester F, Aguilera I, Fernández-Somoano A, Lertxundi A, Llop S, et al. Residential exposure to outdoor air pollution during pregnancy
755 and anthropometric measures at birth in a multicenter cohort in Spain. *Environ Health Perspect*. 2011;119(9):1333–8.

756 11. Fuertes E, Markevych I, Bowatte G, Gruzieva O, Gehring U, Becker A, et al. Residential greenness is differentially associated with childhood allergic
757 rhinitis and aeroallergen sensitization in seven birth cohorts. *Allergy* [Internet]. 2016; Available from:
758 <http://www.ncbi.nlm.nih.gov/pubmed/27087129>

759 12. Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. Development of NO₂ and NO_x land use regression models for estimating
760 air pollution exposure in 36 study areas in Europe - The ESCAPE project. *Atmos Environ*. 2013;72(2):10–23.

761 13. Gruzieva O, Gehring U, Aalberse R, Agius R, Beelen R, Behrendt H, et al. Meta-analysis of air pollution exposure association with allergic sensitization
762 in European birth cohorts. *J Allergy Clin Immunol* [Internet]. 2013/10/08. 2014;133(3):767–76 e7. Available from:
763 <http://www.ncbi.nlm.nih.gov/pubmed/24094547>

764 14. Marie Chavent, Vanessa Kuentz, Amaury Labenne BL and JS. PCAmixdata: Multivariate Analysis of Mixed Data. [Internet]. 2014 [cited 2017 Jun 18].
765 Available from: <https://cran.r-project.org/package=PCAmixdata>