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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

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

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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.

1. Introduction

The prevalence of asthma and allergic conditions is increasing worldwide (Asher, 2011) and has coincided with the rapid and ongoing increase in the percentage of the population residing in urban areas (Gern, 2010). 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 (Brasier, 2014). 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 (Heinrich, 2010). 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 (von Mutius and Vercelli, 2010). These associations have been explained by the 'hygiene hypothesis' (Strachan, 1989); an early, more intense contact to microbial agents might modulate and program the developing of an immune system towards a non-allergic response (Braun-Fahrlander and Lauener, 2003; Lauener et al., 2002). 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 (Strachan et al., 2014; Krämer et al., 2015). 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 (B Campbell et al., 2016). Moreover, early exposure to pets, in particular dogs, has been repeatedly suggested to be associated with a reduced risk of (non-atopic) asthma outcomes (Collin et al., 2015), although overall, associations are inconsistent (Chen et al., 2010; Lodrup Carlsen et al., 2012). 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 (Thacher et al., 2016; Mendell and Kumagai, 2016).

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 (Haahtela et al., 2013; Pilat et al., 2012) as compared to bringing up in rural environments (von Mutius and Vercelli, 2010; Ruokolainen et al., 2015). 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 (Gehring et al., 2015; Molter et al., 2014).

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.

2. Materials and methods

2.1. 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.

2.2. 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.

2.2.1. A-priori approach (main analysis)

2.2.1.1. INDOOR environmental score. Based on Campbell and colleagues (B Campbell et al., 2016), 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* (B Campbell et al., 2016) 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).

2.2.1.2. OUTDOOR-GREEN and OUTDOOR-GREY environmental scores

2.2.1.2.1. Outdoor-green environmental score. We used (i) residential surrounding greenness and (ii) neighborhood 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