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Residential Area Characteristics Are Associated With Asthma Burden in Children

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ABSTRACT

Background: Wheezing illnesses, especially those triggered by rhinovirus infection, cause a major disease burden, and they often precede asthma. Environmental exposures are known to affect recurrence of wheezing. We investigated the relations of population density, greenness (forested areas), and socioeconomic factors of the living surroundings to the burden of asthma in children with prior bronchiolitis.

Methods: Three hundred and ninety-four children, aged 0–24 months, with doctor-diagnosed bronchiolitis were enrolled in the MARC-30 Finland study. We assessed the children's early-life exposures to greenness and socioeconomic factors using time-series of Corine Land Cover data and Statistics Finland's grid data. We compared the living surroundings data to the prescription drug purchases and special asthma reimbursement benefits until the age 8 years; asthma data were from the Social Insurance Institution of Finland.

Results: Children living in sparsely populated areas had lighter asthma disease burden than children living in densely populated ones, with burden measured in median bronchodilator (50DDD [defined daily dose] vs. 104DDD, $p = 0.02$) and inhaled corticosteroid (0DDD vs. 123DDD, $p = 0.04$) purchases. In the subgroup of children with rhinovirus-induced bronchiolitis, children living in more forested areas developed asthma 10 months later than those with less forested areas ($p = 0.04$). Neighborhood socioeconomic characteristics were not associated with differences in asthma burden.

Conclusions: Sparsely populated areas and forested environments seem to have a beneficial association with children's respiratory health. These findings warrant further studies on the protective health effects of greenness and the type of biodiversity around homes.

1 | Introduction

Bronchiolitis, recurrent wheezing, and pediatric asthma constitute a serious disease burden. Although many acute wheezing illnesses and asthma exacerbations are largely viral in origin, the susceptibility to such infections and the propensity to develop asthma seems to depend, at least partially, on environment, allergen and microbe exposure, and host microbiome [1–6]. Alongside environmental and host microbial characteristics, atopic sensitization and genetics are associated with the risk of asthma development [6–11]. Of the bronchiolitis pathogens, several studies have shown that rhinovirus is associated with a heightened risk of subsequent asthma [1, 11].

The effect of green areas around homes on childhood atopy and asthma has been increasingly studied over the past decade [12, 13]. A recent meta-analysis reported that vegetation near homes was negatively associated with childhood asthma risk, with an odds ratio (OR) of 0.88 [14]. In more detailed analyses, farms [15, 16] and natural land-cover types seemed to have a protective effect against asthma [17]. In other studies, however, grass and gardens [18] and coniferous forests [18, 19] were found to be associated with more respiratory disease.

The socioeconomic environment's effect on asthma morbidity also has been studied. Environments characterized by socioeconomic deprivation are associated with increased asthma morbidity [20]. A study conducted in Ohio (USA) reported that the asthma hospitalization rate of children in very low opportunity areas was five times higher than that of children in very high opportunity areas [21]. The mechanisms are still unclear, but these findings are often attributed to less access to healthy lifestyles and proper healthcare [22].

We aimed to investigate the associations between early-life residential area characteristics and asthma prevalence and disease burden among Finnish children who had been hospitalized for bronchiolitis. Finland is the most forested country in Europe—its land cover is 75% forest. We hypothesized—according to the biodiversity hypothesis [23]—that children living in the most sparsely populated and most green areas, and in the most socioeconomically advantageous neighborhoods, would develop asthma later and less frequently and would bear a lower disease burden.

2 | Methods

2.1 | Study Subjects

This study consisted of 394 children who were part of the 30th Multicenter Airway Research Collaboration [MARC-30] Finland [11]. MARC-30 USA was a prospective cohort study conducted by the Emergency Medicine Network in Boston (USA) and MARC-30 Finland was run parallel to the US study but in Finland. Finnish children were recruited from the pediatric wards or intensive care units of three university hospitals in Finland (Kuopio, Tampere, and Turku) during winter seasons from 2008 to 2010 and were hospitalized for bronchiolitis. The children were under 24 months of age at the time of admission and were diagnosed with bronchiolitis based on American Academy of Pediatrics guidelines [24]. All children were defined as having severe bronchiolitis due to their hospitalization. The study was approved by the Institutional Ethical Board of Turku University Hospital and was confirmed by the ethical boards of other participating hospitals. The guardians of the children gave their written informed consent to enter the study [25].

2.2 | Data Collection

During the initial hospitalization, the guardians of the children were interviewed using a structured questionnaire that collected demographic, environmental, and medical information. Information on the signs, symptoms, and treatment of the current infection was documented [25]. Nasopharyngeal samples were obtained. Nasopharyngeal sampling and laboratory methods are described in detail in Supporting Information: S3.

2.3 | Outcomes

The primary outcome was asthma burden, which was defined as the cumulative use of inhaled asthma medications measured in defined daily doses (DDD). We equated drug purchases with drug consumption.

The secondary outcomes were time to asthma onset and prevalence of asthma at age 7 years. We defined the time to asthma onset as the time to the beginning of the special reimbursement benefit. We considered the granting of asthma special reimbursement benefit at any point of life as the presence of asthma. We assessed separately asthma at 7 years of age, which was defined as a valid special reimbursement benefit at that age, and asthma medication purchases within 1 year before that age. Furthermore, we analyzed asthma medicine use at 7 years of age, which was defined as asthma medicine purchases 1 year before that age.

2.4 | Drug Purchases and Special Reimbursement Benefits

Kela, the Social Insurance Institution of Finland, records all prescription drug purchases. Kela also administers reimbursements on prescription drugs and a patient is justified to receive a disease-specific special reimbursement benefit if the child fulfills the criteria. For asthma, the granting of special reimbursement benefits necessitates an accurate diagnosis of asthma and an ongoing (at least 6-month-long) treatment with inhaled anti-inflammatory drugs. Additional details on the diagnostic criteria are found in Supporting Information: S2.

Kela's information services fetched the patients' special reimbursement statuses and the patients' asthma medication purchases from their births until the year 2017. The ATC (Anatomical therapeutic chemical) class we considered as asthma medication was R03.

2.5 | Cumulative Exposure to Residential Area Characteristics

The geocoded residential addresses with dates of moves for the first 2 years of the children's lives were obtained from the Digital and Population Data Services Agency and positioned to the Statistics Finland 250 × 250 m Grid Database. Each environmental index was calculated within this predefined grid. For the analyses, we used the mean of the home grid and the eight adjacent grids, capturing a 750 × 750 m grid size around the homes of the families. To assess the residential environment of the child, we used the amount of forest as an index of green space in the area and population density and neighborhood disadvantage as indices of neighborhood socioeconomic composition.

To calculate the amount of forest around the residential location, we used information on the land cover from CORINE Land Cover data sets of the year 2012. The 12 land cover types include: (1) Residential area, (2) Industrial/commercial area, (3) Transport network, (4) Sport/leisure, (5) Agriculture, (6) Broad-leaf forest, (7) Coniferous forest, (8) Mixed forest, (9) Shrub/grassland, (10) Bare surface, (11) Wetland, and (12) Water bodies. From this information, we calculated a vegetation cover index for broad-leaf forest, coniferous forest, and mixed forest (percentages of these land cover classes in the grid area).

Data regarding population density and neighborhood disadvantage was derived from the grid database established and maintained by Statistics Finland. The database contains socioeconomic information from each residence at a spatial resolution of 250 × 250 m (Statistics Finland, 2013). The population density score is based on the number of individuals living in each 250 × 250 m grid area. The neighborhood disadvantage score is based on the proportion of adults with low education, the unemployment rate, and household income in each 250 × 250 m grid area. For each of the three variables, we derived a standardized z-score based on the total Finnish population (mean = 0, SD = 1). A score for neighborhood disadvantage was then calculated by taking the mean value across the three z scores. Higher scores on the continuous index denote greater socioeconomic disadvantage [26].

2.6 | Statistical Methods

Statistical analyses were conducted using SPSS version 26.0.0.0 (IBM Corporation, Armonk, NY, USA). We divided the children into four equal-sized quartiles based on the environmental metrics and compared the two extreme quartiles—that is, the children having cumulatively the least and most populous living environments, children having cumulatively the least and most forested living environments, and children having cumulatively the least and most disadvantaged neighborhoods, respectively. Continuous data were analyzed by independent samples T-test when the data were normally distributed, and by Mann–Whitney, test when the data were non-normally distributed. Categoric data were analyzed by the Chi-square test or Fisher's exact test (when cell counts were < 5). A two-tailed $p < 0.05$ was considered statistically significant. Linear correlations were expressed using Pearson's correlation coefficient.

3 | Results

3.1 | Study Cohort

Four hundred and eight children took part in the MARC-30 Finland study, and 403 gave their permission to fetch their prescription drug purchases and special reimbursement benefits from Kela. We were able to fetch the address histories of 394 children from the Digital and Population Data Services Agency.

3.2 | Patient Characteristics

The 394 children were divided into equal quartiles based on the size of population around their homes. Most children admitted for bronchiolitis were boys (61%). The groups did not differ in terms of age, history of asthma, parental asthma, adherence to the national vaccination program, body weight, vitamin D supplement use, history of breastfeeding, daycare arrangement, exposure to smoking during pregnancy or at home, detected pathogens, antibiotics administration, nor systemic corticosteroid administration. The children of the least populous quartile were more likely to live with their fathers and with other children. The children in the most populous quartile were more likely to present with cough and lower oxygen saturation during the initial hospitalization, and they were more likely to live in the Tampere University hospital region. The children in the least populous quartile were more likely to live in the Kuopio University hospital region. (all $p < 0.05$, Table 1).

3.3 | Asthma Burden

We compared the purchases of asthma medications from the birth until the age of 8 years. Children living in the most sparsely populated areas consumed less inhaled corticosteroids (ICS) (5% trimmed mean 122DDD vs. 202DDD, $p = 0.04$) and bronchodilators (5% trimmed mean 97DDD vs. 154DDD, $p = 0.02$) than the children living in the most densely populated areas over the 8-year period (Figure 1).

Children living in the most forested areas consumed less ICS (5% trimmed mean 22DDD vs. 43DDD, $p = 0.02$) and bronchodilators (5% trimmed mean 27DDD, $p = 0.02$) than the children in the least forested areas in the first 2 years of life. Over the entire 8-year period, the consumptions did not differ.

In the subgroup of 62 children with rhinovirus-induced bronchiolitis, sparser population density was associated with lower bronchodilator purchases in the first 3 years (5% trimmed mean 116DDD vs. 163DDD, $p = 0.045$) and lower ICS purchases in the first year of life (5% trimmed mean 50DDD vs. 78DDD, $p = 0.03$). Later, the purchases did not differ.

In rhinovirus-only children, the bronchodilator purchases over the first 4 years were lower (5% trimmed mean 132DD vs. 215DDD, $p = 0.050$) in children who lived in the most forested surroundings compared to children who lived in the least

TABLE 1 | Proportions of detected viruses did not differ between the groups. Additional data on viral detection in Supporting Information: S1.

Characteristic (*n*)	Most sparsely populated quartile ($n = 99$)	Most densely populated quartile ($n = 98$)	*p*-Value
Background			
Male, *n* (%)	58 (59%)	58 (59%)	0.9
History of asthma, *n* (%)	5 (5%)	6 (6%)	0.7
History of wheezing, *n* (%)	32 (32%)	37 (38%)	0.4
History of atopic dermatitis, *n* (%)	29 (29%)	20 (20%)	0.2
Vaccinated as recommended, *n* (%)	93 (94%)	90 (92%)	0.6
Parental asthma, *n* (%)	20 (20%)	26 (27%)	0.3
Maternal smoking during pregnancy, *n* (%)	9 (9%)	16 (16%)	0.3
History of breastfeeding, *n* (%)	92 (93%)	90 (92%)	0.5
Environment			
Other children living at home, *n* (%)	83 (84%)	61 (62%)	**0.001**
Number of children living at home, median (range)	3 (1–9)	2 (1–6)	**< 0.001**
Daycare outside of home, *n* (%)	14 (14%)	19 (19%)	0.3
Mother lives at home, *n* (%)	97 (98%)	95 (97%)	0.7
Father lives at home, *n* (%)	95 (96%)	83 (85%)	**0.008**
Is the child subjected to secondhand smoke, *n* (%)	2 (2%)	6 (6%)	0.2
Vitamin D supplement, *n* (%)	88 (89%)	88 (90%)	0.6
Study site Turku, *n* (%)	30 (30%)	39 (40%)	0.2
Study site Tampere, *n* (%)	28 (28%)	41 (42%)	**0.046**
Study site Kuopio, *n* (%)	41 (41%)	18 (18%)	**< 0.001**
Presentation and treatment			
Age, months; mean, (range)	8.5 (0–24)	9.6 (1–23)	0.3
Weight, kg; median (range)	8.1 (2.3–15)	8.4 (3.7–15)	0.2
Temperature, median (range) (°C)	37 (36–40)	37 (36–40)	0.2
Heart rate, median (1/min)	152 (85–195)	160 (75–200)	0.3
Respiratory rate, median (1/min)	63 (9–80)	60 (22–90)	0.3
Oxygen saturation, median (%)	96 (86–100)	95 (78–100)	0.2
Preceding cough, *n* (%)	50 (55%)	78 (81%)	**< 0.001**
Preceding wheezing, *n* (%)	61 (62%)	76 (78%)	0.2
Human rhinovirus, *n* (%)	27 (27%)	35 (36%)	0.2
Respiratory syncytial virus, *n* (%)	48 (49%)	44 (45%)	0.6
Other virus, *n* (%)	28 (28%)	25 (26%)	0.7
Received systemic corticosteroids, *n* (%)	15 (15%)	25 (26%)	0.07
Received antibiotics, *n* (%)	6 (6%)	7 (7%)	0.6

forested environment. This association was present until the fourth birthday, after which the purchases did not differ. The ICS purchases did not differ over the 8-year observation period.

Neighborhood disadvantage was not associated with differences in ICS or bronchodilator purchases neither in the overall population nor the rhinovirus-only subgroup.

3.4 | Time to Asthma

In the overall study population, differences in the environmental factors were not associated with differences in time to asthma although forests around homes were marginally associated with a delay in asthma inception (median 24 months vs. 32 months, $p = 0.054$).

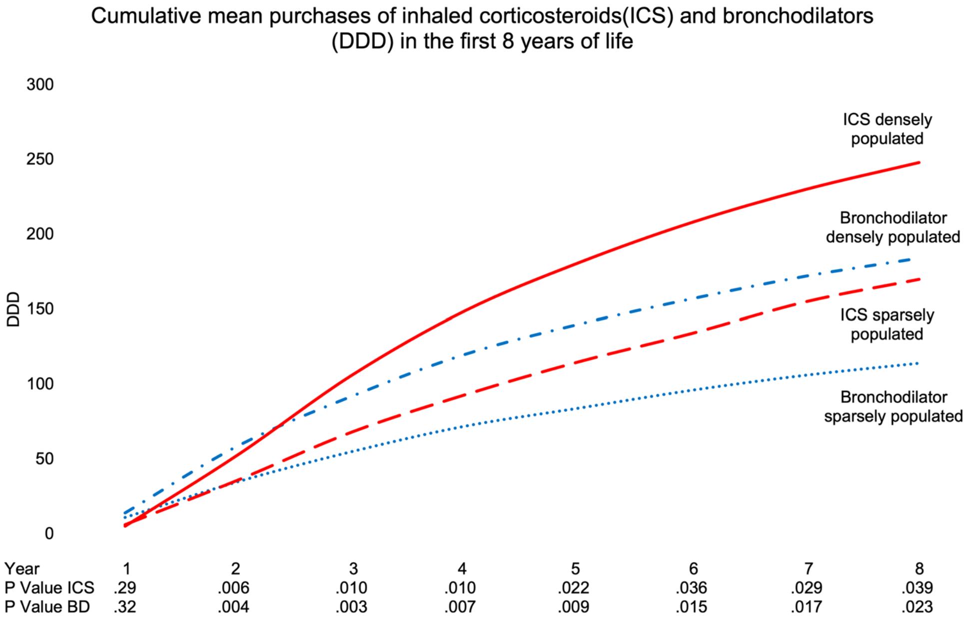

FIGURE 1 | Cumulative mean purchases of inhaled corticosteroids and bronchodilators in the first 8 years of life of children in the most and least densely populated quartiles.

In a subpopulation of children with rhinovirus-induced bronchiolitis, forests around homes were associated with a delay in granting of asthma special reimbursement benefits (median 24 months vs. 34 months, $p = 0.04$). Neither population density nor neighborhood disadvantage was associated with age at special reimbursement benefit begin in rhinovirus subpopulation.

3.5 | Prevalence of Asthma

Overall asthma prevalence was 33%. Neither population density, nor forestation, nor socioeconomic factors were associated with differences in overall asthma prevalence.

Proportion of children with asthma at 7 years was 15%. Forestation, population density, and socioeconomic disadvantage were not associated with differences in asthma prevalence at 7 years.

The percentage of children using asthma medication at age 7 years was 32%. There were no differences associated with population density, forestation, nor socioeconomic disadvantage.

In children with rhinovirus-induced bronchiolitis, population density, forestation, nor neighborhood disadvantage were associated with differences in overall asthma prevalence, asthma at 7 years, or number of asthma medication users at 7 years.

3.6 | Correlations Between the Residential Area Characteristics

The population density had a weak inverse correlation with forestation: $R(392) = -0.23$, $p < 0.001$. Neighborhood disadvantage and population density were weakly correlated: $R(392) = 0.21$, $p < 0.001$. Forestation and neighborhood disadvantage had a weak negative correlation: $R(392) = -0.12$, $p = 0.02$.

4 | Discussion

To our knowledge, there are no prior cohort studies that investigate the association between living environments and respiratory morbidity in children after hospitalization for bronchiolitis. The current results suggest that bronchodilator and inhaled corticosteroid purchases and thus asthma morbidity were lower among children living in more sparsely populated areas and that proximity of forest was associated with delay of asthma inception in the high-risk subgroup of children with rhinovirus-induced bronchiolitis. Socioeconomical differences were not associated with disparities in asthma burden in this study and, consequently, do not explain the observed environmental differences for asthma.

Forest with its microbiologically diverse dirt and vegetation may have more favorable effects on a child's immunotolerance than man-made yards and green areas, which is supported by earlier reports [27, 28]. Also, urbanization has been shown to reduce the transfer of microbiota indoors [29]. In light of our findings, we speculate, that children living in sparsely populated neighborhoods and close to forests are exposed to richer and more diverse microbiota, which might favorably affect their disease course.

Rhinovirus-induced bronchiolitis is the most potent asthma risk marker [1, 10]. The novel finding about the potential benefit of proximity to forest is of potential clinical importance; all measures, which can alleviate asthma burden are welcome. Certainly, not all families can live surrounded by forests but in Finland, forests are readily accessible to everyone, and spending time in forests or other biodiverse environments [27] might be beneficial. The children's exposure to forests might also be influenced by urban planning, that is, new daycare facilities, schools, or recreational facilities could be established in nearby forests so that the time spent in biodiverse environment would be frequent and continued.

That there were no differences in asthma prevalence and drug purchases found between the most disadvantaged and advantaged areas might be due to well-organized universal healthcare and the comparatively extensive Finnish welfare state. Finland is a remarkably equal society: by Gini coefficient, Finland was the 14th most equal country out of 177 countries listed [30].

This study has several strengths: it is based on a prospective cohort, which was carefully characterized at study entry and with 97% follow-up at 7 years. The virus etiology of bronchiolitis was defined by modern techniques and the research sites were university hospitals. Instead of assessing the environment using the normalized difference vegetation index (NDVI), which is based on satellite records of the absorption of certain sunlight wavelengths by plants, we used CORINE land cover data, which is based on interpreted satellite images, and it can better capture the characteristics of the environment than NDVI. The Finnish system of prescription drug reimbursements and special reimbursement benefits enabled us to fetch the drug purchases nationwide and reliably compare the asthma burden between different groups of children.

The study has also some limitations including relatively small sample size, although the prospectively recruited cohort represents the wheezing-wise relevant population well. Furthermore, the asthma diagnoses were not objectively verified by the study physician, but we think that the strict and well-defined national reimbursement criteria requiring ongoing regular asthma controller medication for more than 6 months is a rather strong indication of asthma. Also, the data on the bronchodilator and asthma-controlling medication purchases are consistent with one another, which we find reassuring. We acknowledge that data on asthma-related hospitalizations, visits to the emergency department, and visits to the general practitioner or pediatrician would be of high interest but unfortunately, we did not have access to those data but rely on asthma drug purchases as a surrogate measure of asthma burden. One additional limitation of the study is that we did not have the possibility to analyze the air pollutants of the living environments, which could have allowed us to discover if the benefits associated with sparsely populated areas and forests could be found independent of the air pollution. In Finland, levels of some air pollutants have been found to be lower near forests [31].

In conclusion, exposure to nature might be beneficial to children, especially to children at risk for developing asthma. Our data showed that early life spent in sparsely populated and forested areas was associated with beneficial respiratory health effects in children after bronchiolitis. These findings warrant further studies on the protective health effects of greenness and biodiversity around homes.

Author Contributions

Riku Erkkola: conceptualization, methodology, software, data curation, writing–original draft, writing–review and editing, visualization, validation, formal analysis, investigation, project administration. **Carlos Gonzales-Inca:** conceptualization, methodology, data curation, validation, formal analysis, software, writing–review and editing, investigation. **Jussi Vahtera:** conceptualization, methodology, investigation, writing–review and editing. **Eija Bergroth:** writing–review and editing, conceptualization, investigation, methodology, data curation. **Matti Korppi:** writing–review and editing, investigation, conceptualization, methodology. **Carlos A. Camargo:** writing–review and editing, conceptualization, methodology, investigation. **Tuomas Jartti:** writing–review and editing, supervision, project administration, conceptualization, investigation, methodology, validation, funding acquisition, writing–original draft, resources.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data not available. The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.