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Associations between Neighbourhood Greenness and Asthma in Preschool Children

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ABSTRACT

Objectives: The aim of this study was to investigate the associations between surrounding greenness levels and asthma among children, and to explore possible modification of this association by the distance of the residence to a city park.

Design: A nested case-control study.

Setting: Children of 4−6 year's age residing in Kaunas, Lithuania, who were recruited 2007-2009 to the KANC newborns cohort study.

Participants: 1,489 children whose parents in 2012-2013 filled in the questionnaires and agreed to participate in the study.

Primary and secondary outcome measures: We estimated clinically diagnosed asthma risk factors. The surrounding greenness was measured as the average of the satellite-based Normalized Difference Vegetation Index (NDVI) within the buffers of 100, 300, and 500 m from each child's home, and the distance to a city park was defined as the distance to the nearest city park. Multivariate logistic regression was performed to study the relationship between the greenness exposures and asthma adjusted for relevant covariates.

Results. An increase in the NDVI (>median) in buffers of 100, 300, and 500 m was associated with a slightly increased risk of asthma, while an interquartile range increase in NDVI-100 m statistically significant increased the risk of asthma (OR 1.43, 95% CI 1.10−1.85). The stratified analysis by surrounding greenness revealed indications of stronger associations for children with higher surrounding greenness (NDVI-100>median) and those living farther away from parks (>1000 m), compared to NDVI-100≤median and the distance to a city park >1000 m (OR 1.47, 95% CI 0.56−3.87*)*.

Conclusions. Higher level of the surrounding greenness was associated with a slightly increased relative risk of asthma in children. Further investigation is needed to elucidate the influence of city parks and neighbourhood greenness levels on asthma.

Keywords: Child asthma, green spaces, city park

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The current epidemiological study had the advantage of using a large number of covariates gathered during the interview, and the objective individual-level estimation of exposure to green spaces and major ambient air pollutants.
- This is the first study in Eastern Europe demonstrating the associations between greater quantity of greenness in the 100 m buffer size of home, assessed at an individual level, and the increased risk of asthma in children.
- The interaction analysis of surrounding greenness and distance to parks on asthma risk showed a slight additive effect.
- The modifying effect of the surrounding greenness and the distance to city parks on childhood asthma controlling for PM2.5 and NO2 influence has not been previously studied; therefore, further investigations are needed to confirm this case-control study results.

INTRODUCTION

Asthma is the most prevalent chronic disease among children. Over the last decades, the prevalence of asthma has progressively increased in the industrialized world and in developing regions.[1, 2] There is large geographical variation in the prevalence of asthma ranging from less than 2% to more than 20% in some countries.[3, 4] The majority of the causative agents of asthma in children remains uncertain and need clarification. Asthma likely depends on a number of interacting factors, including genetic, behavioural and environmental risk factors,[5-8] including long-term exposure to urban air pollutants emitted by traffic.[9]

During the last decade, more attention has been devoted to the studies on the impact of the surrounding environment on allergies and asthma seeking to elucidate the role of urban green spaces in childhood chronic diseases.[10, 11] Epidemiologic data on the influence of green spaces on allergy and asthma in children are limited and inconsistent. While some studies have reported an unfavourable influence of green spaces on the prevalence of asthma and the exacerbation of allergic conditions,[10, 12] others have reported no relationships between greenery assessed as the Normalized Difference Vegetation Index (NDVI), canopy cover, and asthma.[13, 14] A protective effect of the green environment around homes on the risk of atopic sensitization in children was also founded possible due to increase biodiversity.[15, 16] There is mounting evidence that the close distance from place of residence to city parks and visiting green space has benefits for people's health.[17-19]

Inconsistent associations between green space exposure and childhood asthma have stimulated studies of the interactions between the surrounding greenness levels, the distance of the place of residence to city parks, and asthma. This is the first study in Eastern Europe evaluating the impact of quantified greenness levels in the urban environment on the risk of asthma in 4−6 year-old children. In the present study, using individual-level data of a population-based sample and adjusting for important risk factors for asthma, we investigated the associations between objectively estimated residential greenness levels as the NDVI, residential distance to the nearest city park (>1 ha), and the number of children clinically diagnosed with asthma controlling for various covariates. Furthermore, we investigated the interaction between surrounding greenness, distance to a city park and the risk of asthma in children.

MATERIALS AND METHODS

This study was conducted as part of the Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe (PHENOTYPE) project funded by the European Commission Seventh Framework Programme.[11] We used Kaunas city pregnant women data that were recruited 2007-2009 to the KANC newborns cohort study. In 2012-2013 we invited 3,294 mothers and their 4−6 year's old children to participate in this study. We receive response to the questionnaire sent by post from 1,489 mothers (response rate 45.2%). The participants of this research were children whose parents or guardians filled in the questionnaires and agreed to participate in the study. The study was approved by the Lithuanian Bioethics Committee, and parental informed consent was obtained from all participants. Questionnaire responses by parents or guardians were used to categorise children's basic information, medical history, family history, personal habits, children's height and weight, and housing and environmental conditions. Responses to the standardised International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents were used to identify children with asthma. Childhood asthma was identified by an affirmative response to the question: "Has you child ever had doctor-diagnosed asthma?" Cases (n = 112) were children with clinically diagnosed asthma. Controls (n = 1,377) were children without an asthma.

Assessment of exposure to green spaces

Exposure to green spaces was objectively estimated for every child's home addresses using a standardized protocol and assuming that a shorter distance to a city park or a higher NDVI represents a greater exposure to green spaces. In 2012-2013 all children addresses were geocoded to the exact address according to the street name, and house number. Kaunas city green space was defined by LANDSAT_5 Thematic Mapper (TM) images at 30 m×30 m resolution retrievals and the NDVI was assigned to individuals' place of residence. The map of the NDVI was generated using the image that was obtained on July 2011. Mean NDVI values of a straight-line buffer were calculated as estimations of the level of greenness within the immediately accessible neighbourhood (100, 300, and 500 m) of every home where various kind of pollen may be expected.

Using the Urban Atlas data for Kaunas city, we estimated the straight-line distance from every participant's home to the nearest city park larger than 1 ha; most of them had 65% of the area covered with trees. In the parks and squares 195 species and cultivars of introduced ligneous plants are registered (42 are *Pinophyta*, 153 are *Magnoliophyta*).[20] All the parks are open to the public and offer similar recreation opportunities (e.g. walking, jogging, rollerblading, physical training, or resting on the bench) and locations (located among residential homes or establishments), and near public transport lines producing good possibility contact of children with environmental biodiversity.

To evaluate the possibility that ambient air pollution may confound associations between green spaces and asthma, we modeled a home address-specific measures of fine particulate matter ($PM_{2.5}$), and ambient concentrations of nitrogen dioxide (NO_2). During the statistical analysis exposure to $PM_{2.5}$ and NO_2 was categorized by median.

Statistical analysis

We used chi-square and univariate logistic regression analyses to compare the values and frequencies of the baseline characteristics by the studied children's asthma status. Predictor variables whose univariate test showed a statistically significant association ($P<0.05$) with the outcome - or those that changed the adjusted odds ratios (aOR) by 10% or more - were retained for the inclusion in multiple logistic regression analyses. The NDVI, our indicator of residential greenness, was modeled both as a continuous (interquartile range) and categorical (by median) measure. Using logistic regression analysis, we estimated the association between residential greenness in 100, 300, and 500 m buffers by median and interquartile range (IQR) and asthma as crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI). To determine how the associations between residential surrounding greenness and asthma changed based on the distance to parks, the effect modification of the NDVI-100 m (100 m buffer around each maternal home) median and a 1000-meter distance to a park was assessed by including an interaction term in the logistic regression controlling for covariates that may influence the risk of asthma. Odds ratios were adjusted for individual-level mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping cat during the last 12 months, living in a flat, and ambient $PM_{2.5}$, and NO_2. All statistical analyses were performed using SPSS software version 18.0.

RESULTS

Characteristics of the study population

Of In 2012-2013, we were able to geocode home addresses and estimate residential greenness exposure for 1,489 4−6 year's old children (response rate 45.2%) of 3,294 KANC new-borns cohort who mothers returned questionnaires. The demographic variables of those women who did not respond to the questionnaire were not statistically significantly different from the participants with regard to the birth outcomes and covariates (data not shown). Of the 1,489 study children with complete data, 81.7% had homes located within 1000 meters from the nearest city park (10−15 minutes walking distance). Regarding the surrounding greenness level, the medians (IQR) of the mean NDVI across the buffers of 100, 300, and 500 m around the places of residence were 0.553 (0.110), 0.548 (0.109), and 0.547 (0.116), respectively. The mean annual residential greenness values of the 25th, the 50th, and the 75th percentiles are presented in Table 1. The median (minimum and maximum) of ambient NO2 was 15.85 μg/m3 (8.85−31.05 μg/m3) and PM2.5– 20.44 μg/m3 (15.83–36.09 μg/m3) for residential addresses.

Table 1. Distribution of residential greenness level in different buffers size

Variable	25th	Median	75th	IQR
NDVI-100 m	0.489	0.553	0.599	0.110
NDVI-300 m	0.494	0.548	0.602	0.109
NDVI-500 m	0.491	0.547	0.608	0.116

Physician-diagnosed asthma was reported in 112 (7.5%) children, of whom 91 (81.3%) were living within the 1000-meter buffer zone of the nearest city park.

The descriptive statistics for the characteristics of asthmatic and non-asthmatic children and the prevalence of the investigated variables are presented in Table 2. In general, asthma was more prevalent among 4–6 year-old children whose mothers were less educated, suffered from asthma, was smoking during pregnancy or was exposed to environment tobacco smoke, was living in a flat, or whose children used antibiotics during the first year of life. Children with asthma less time spent in green space than healthy children.

Table 2 Distribution of variables according to children's asthma status

Variables	Asthma yes N (%)	Asthma no N (%)
Mother's age at childbirth		
<30	71 (7.1%)	924 (92.9%)
31 and more	41 (8.3%)	454 (91.7%)
Maternal education status		
Low (10 or fewer years)	33 (10.7%)*	274 (89.3%)
Medium and high (>10 years)	79 (6.7%)	1103 (93.3%)
Social-economic status		
Low	35 (8.7%)	366 (91.3%)
Medium, High	77 (7.1%)	1011 (92.9%)
Maternal smoking during pregnancy		
No	98 (7.1%)	1278 (92.9%)
Yes	14 (12.4%)	99 (87.9%)
Maternal passive smoking		

No	66 (6.9%)	890 (93.1%)
Yes	46 (8.6%)	487 (91.4%)
Gas cooking		
No	34 (6.4%)	501 (93.6%)
Yes	78 (8.2%)	876 (91.8%)
Living in a flat		
No	41 (6.7%)	568 (93.3%)
Yes	71 (8.1%)	809 (91.9%)
Sex		
Male	63 (8.5%)	675 (91.5%)
Female	49 (6.5%)	702 (93.5%)
Birth order		
1	56 (6.8%)	766 (93.2%)
2 and more	56 (8.4%)	611 (91.6%)
Breastfeeding		
No	11 (11.1%)	88 (88.9%)
Yes	101 (7.3%)	1289 (92.7%)
Paracetamol use during the first year of life		
No	27 (6.0%)	426 (94.0%)
Yes	85 (8.2%)	951 (91.8%)
Antibiotic use during the first year of life		
No	50 (5.1%)	924 (94.9%)
Yes	62 (12.0%)*	453 (88.0%)

Asthma in parents		
No	91 (6.5%)	1300 (93.5%)
Yes	21 (21.4%)*	77 (78.6%)
Time spent in green space		
≤5 hours	70 (8.5)	753 (91.5)
>5 hours	42 (6.3)	624 (93.7)

* p<0.05.

Association between green space and asthma

The proportions of children with asthma had a tendency to increase with an increasing median NDVI in different buffer sizes (Table 3). In addition, the NDVI higher than the median was associated with a 27%, 19%, and 32% increase in the probability of asthma within 100, 300, and 500 m of residences, respectively, in unadjusted models. After adjustment, the associations were similar, yet not statistically significant. The associations of NDVI interquartile range in NDVI-300 m and NDVI-500 m buffer sizes with asthma were similar in magnitude. However, an increase in the interquartile range of green space, using the NDVI-100 m buffer size, was associated with a statistically significant increase in the asthma risk after adjustment for parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, and time spent in green space (aOR 1.43, 95% 1.10−1.85). The distance to a park was not associated with the increased risk of asthma when was analysed total sample.

Table 3 Unadjusted and adjusted effects of green spaces as asthma odds ratios (OR) and 95% confidence intervals (CI)

Exposure	Asthma yes	Unadjusted	Adjusted†

variables	N (%)	OR (95% CI)	OR (95% CI)
NDVI-100			
≤median	50 (6.7)	1	1
>median	62 (8.4)	1.27 (0.85−1.91)	1.19 (0.79−1.79)
IQR‡		1.43* (1.12−1.82)	1.43* (1.10−1.85)
NDVI-300			
≤median	52 (6.9)	1	
>median	60 (8.1)	1.19 (0.79−1.78)	1.17 (0.78−1.76)
IQR‡		1.21 (0.95−1.56)	1.23 (0.94−1.61)
NDVI-500			
≤median	49 (6.6)	1	1
>median	63 (8.5)	1.32 (0.88−1.98)	1.39 (0.92−2.10)
IQR‡		1.15 (0.88−1.50)	1.18 (0.88−1.57)
Distance to a city park			
>1000 m	21 (7.7)	1	1
≤1000 m	91 (7.5)	0.97 (0.59−1.59)	0.96 (0.55−1.68)

†Adjusted for: parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, time spent in green space.

‡IQR interquartile range increase.

* $p<0.05$.

Effect modification by surrounding greenness and distance to city parks

We performed the stratified analysis by NDVI-100 and distance to a city park and studied the possible modifying effect of greenness on the risk of asthma among children. The interaction term included the NDVI-100≤median as a reference, and the distance to a city park >1000 m − as effect modifier (Table 4). In the sensitivity analysis asthma risk estimates were essentially unchanged after adjustment for maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma, maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding, living in a flat. After additional adjusting for $PM_{2.5}$, and NO_2, we found the risk of asthma to be by 15% higher among children residing close to city parks (≤1000 m) in areas with low exposure to green spaces (NDVI-100 m below median); however, the effect modification for an increased risk of asthma was not statistically significant (adjusted OR 1.15; 95% CI 0.50–2.62).

Table 4 The modifying effect of NDVI−100 m buffer, distance to a city park, and clinically diagnosed asthma in 4−6 year-old children

100 m buffer NDVI & distance to a city park	Asthma cases No (%)	Unadjusted OR	Adjusted† OR (95% CI)
NDVI-100 ≤median & to city park >1000 m	9 (6.5)	1	1
NDVI-100 ≤median & to city park ≤1000 m	41 (6.7)	1.04 (0.47−2.37)	1.15 (0.50−2.62)
NDVI-100 >median & to city park >1000 m	12 (9.0)	1.42 (0.54−3.81)	1.47 (0.56−3.87)
NDVI-100 >median & to city park ≤1000 m	50 (8.2)	1.30 (0.60−2.91)	1.27 (0.56−2.86)

†Adjusted for: maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma, maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding, living in a flat, $PM_{2.5}$ and NO_2.

When comparing the effect of NDVI below the median with that above the median within the 100 meter buffer size from home among children with low park exposure (distance to a city park >1000 m), we found that the risk of asthma increased by 47%, and for those living closer to a park, the risk of asthma increased by 27% (adjusted OR 1.27, 95% CI 0.56–2.86). The unadjusted and adjusted results showed that higher greenness levels measured within a 100 meter buffer size of the home had a higher effect on the risk of asthma among 4−6 year-old children than residence closer than 1000 m to a city park did; however, these results were not statistically significant.

DISCUSSION

The results of this nested case-control study present some evidence for our hypothesized modification of the association of the surrounding greenness levels, the distance from the place of residence to city parks, and clinically diagnosed asthma in children. Regression models adjusted for covariates indicated that an interquartile increase in greenness within 100 m of the surrounding maternal home address was associated with a 43% increase in asthma risk at 4–6 years of age; while close residence to a city park was not statistically significant associated with asthma risk.

These patterns of the associations, assessed at an individual level, are consistent with the previous reports that found a higher relative prevalence of current asthma associated with living close to parks[13] or higher street tree canopy coverage.[9] However, no statistically significant relationships between the tree canopy coverage and asthma rates were found in a Texas study.[14] Previously, in an ecological-design study, an inverse association was observed between an increase in street tree density and a decrease in the prevalence of asthma among children in urban areas such as New York City,[15] yet this does not permit an inference that trees are causally related to the prevalence of asthma at the individual level.

The difference in tree species and park plant biodiversity may have an impact on the observed different levels of associations between residential distance to forests and to parks and the prevalence of childhood asthma.[13, 21] Also, a difference between forest and park flora and the composition of their pollens could explain these variations.[10, 12, 22] A clinical study in Korea showed that short-term exposure to forest environment may have positive clinical and immunological effects in children with allergic diseases who were living in the urban community.[23] Furthermore, residential location, social factors, age, and education are likely to have an impact on the use of green spaces and the course of allergic diseases.[24, 25] By reducing noise and air pollution levels, enhancing physical activity, and minimizing sedentary life style, greenness may have a positive impact on the reduction of psychophysiological stress in children residing in poorer housing and environmental conditions.[26-28]

Some of our observed associations between higher residential greenness levels and an increased risk of asthma are consistent with the results of the previous studies, while others are not. In a New York city cohort study, asthma among 7 year-old children increased by 17% per standard deviation increase of tree canopy coverage (adjusted risk ratios 1.17; 95% CI 1.02–1.33).[14] The results of this study are in line with those of the previous studies, suggesting that high exposure to green spaces may increase the risk of allergic conditions and the prevalence of asthma through the production of pollen.[10, 12] On the other hand, the decrease in the biodiversity of the living environment has been associated with dysfunctions of the immune system and increasing allergies.[21, 29] A study of schoolchildren in Sabadell, Spain, concluded that an interquartile range increase in residential surrounding greenness was not associated with current asthma.[13] No statistically significant relationships between NDVI and the prevalence of asthma were found in an ecological study, which did not control for possible confounding covariates.[14] However, cohorts from Finland and Estonia reported that the amount of green environment around homes was inversely associated with the risk of atopic sensitization in children 6 years of age and older.[16] The authors concluded that environmental biodiversity affects the composition of the human skin microbiota, influences immune tolerance, and decreases the risk of atopic sensitization in children.

We found stronger associations for asthma among children exposed to higher surrounding greenness than for those living close to city parks. The interaction analysis showed that there is an additive effect of surrounding greenness and distance to parks; therefore, in the areas with low greenness levels, the effect of park distance might became more prominent.

The modifying effect of the surrounding greenness and the distance to city parks on childhood asthma controlling for PM2.5 and NO2 influence has not been previously reported. Both psychophysiological stress reduction and increased physical activity have been suggested to explain the associations between green space and better health, but so far there is no clear understanding of the impact of the exposure to green spaces on allergy and asthma in children.[11, 30] Heterogeneous associations of residential greenness with allergic conditions further emphasize that the effect of green spaces on health is complex and needs to be further investigated across studies that vary in the composition of green spaces, air quality, and population groups.

In this study, measurement errors may be present in the evaluation of health outcomes, and the estimations of the associations may be skewed by unmeasured confounding data obtained by parents' responses to questions on their children's asthma, as well as by variables that could have resulted in the misclassification of health outcomes and might have attenuated the strengths of the observed associations. However, this limitation is assumed to be random. The results are also affected by the small sample sizes used in the stratified analysis, which may have an impact on the ability to detect a statistically significant relationship.

The current study had the advantage of using a large number of covariates gathered during the interview, and thus may individually control for covariates associated with asthma, such as smoking, maternal diseases, education, and others. Another advantage is the objective estimation of exposure to green spaces and major ambient air pollutants at the individual level and the possibility to assess the interaction effect of the surrounding greenness level and the distance to a park on the risk of asthma. Even though many covariates in the analyses were considered, residual confounding remains possible. Antenatal allergic sensitization, which is the most common precursor to the development of asthma and polymorphisms in inflammation genes might affect the association between environmental exposures and the risk of asthma in early childhood.[7] Additional associations that may be considered in the future research include chronic stress in children and the interaction between the behavioural, genetic, and environmental risk factors that may be related to asthma. The generalizability of our findings may, however, be somewhat limited since possible differences in surrounding greenness exposure and park biodiversity.

CONCLUSIONS

In this study a higher level of the surrounding greenness was associated with a slightly increased relative risk of current asthma in children. This study is one of the first to evaluate the modifying effect of the surrounding greenness in the living environment and the distance to city parks on the risk of asthma among children, and demonstrates positive associations between surrounding greenness quantity and the prevalence of asthma among 4−6 year-old children. Although our findings on the modifying effect of the surrounding greenness and the distance to city parks require further confirmation by other studies, they highlight the need for more research on the effect of the natural environment on children's health. If the relationship between childhood asthma and exposure to green spaces could be conclusively established, this could provide preventive measures for allergy management and intervention programs.

CONTRIBUTORSHIP STATEMENT SA performed statistical analysis, drafted of the methods, and was the lead writer. RG conceived the idea, designed the study, and revised of the manuscript. JK assisted with the writing of the manuscript and revised the manuscript. AB assisted with the writing and revising of the manuscript. MJN conceptualised and supervised the analyses, and critically reviewed the manuscript. All authors critically reviewed and revised the manuscript, and approved the final version of the manuscript as submitted.

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PATIENTS CONSENT Obtained from parents.

ETHICS APPROVAL This study was approved by the Lithuanian Bioethics Committee.

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Associations between Neighbourhood Greenness and Asthma in Preschool Children: a Case-control Kaunas Study

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ABSTRACT

Objectives: The aim of this study was to investigate the associations between surrounding greenness levels and asthma among children, and to explore possible change of this association by the distance of the residence to a city park.

Design: A nested case-control study.

Setting: Children of 4−6 year's age residing at their current address since birth in Kaunas, Lithuania, whose mothers were recruited 2007-2009 to the KANC newborns cohort study.

Participants: 1,489 children whose parents in 2012-2013 filled in the questionnaires and agreed to participate in the study.

Primary and secondary outcome measures: We estimated clinically diagnosed asthma risk factors. The surrounding greenness was measured as the average of the satellite-based Normalized Difference Vegetation Index (NDVI) within the buffers of 100, 300, and 500 m from each child's home address, and the distance to a city park was defined as the distance to the nearest city park. Multivariate logistic regression was performed to study the relationship between the greenness exposures and asthma adjusted for relevant covariates.

Results. An increase in the NDVI (>median) in buffers of 100, 300, and 500 m was associated with a slightly increased risk of asthma, while an interquartile range increase in NDVI-100 m statistically significant increased the risk of asthma (OR 1.43, 95% CI 1.10−1.85). The stratified analysis by surrounding greenness revealed indications of stronger associations for children with higher surrounding greenness (NDVI-100>median) and those living farther away from parks (>1000 m), compared to NDVI-100≤median and the distance to a city park >1000 m (OR 1.47, 95% CI 0.56−3.87*)*.

Conclusions. Higher level of the surrounding greenness was associated with a slightly increased relative risk of asthma in children. Further investigation is needed to elucidate the influence of city parks and neighbourhood greenness levels on asthma.

Keywords: Child asthma, green spaces, city park, quantified greenness levels.

STRENGTHS AND LIMITATIONS OF THIS STUDY

•The current nested case-control study had the advantage of using a large number of covariates gathered during the interview, and the objective individual-level estimation of exposure to green spaces buffers around the home addresses and major ambient air pollutants.

•This is the first case-control study demonstrating the positive associations between greater quantity of greenness in the 100 m buffer size of home, assessed at an individual level, and the increased risk of asthma in children of 4−6 year's age residing at their current address since birth.

•The analysis of the joint effect of surrounding greenness and distance to park on asthma risk controlling for relevant covariates and fine particulate matter (PM2.5), and ambient concentrations of nitrogen dioxide (NO2) showed a slight additive effect on the strength of association; therefore, further investigations are needed to confirm this nested case-control study results.

INTRODUCTION

Asthma is the most prevalent chronic disease among children. Over the last decades, the prevalence of asthma has progressively increased in the industrialized world and in developing regions.[1, 2] There is large geographical variation in the prevalence of asthma ranging from less than 2% to more than 20% in some countries.[3, 4] The majority of the causative agents of asthma in children remains uncertain and need clarification. Asthma likely depends on a number of interacting factors, including genetic, behavioural and environmental risk factors,[5-8] including long-term exposure to urban air pollutants emitted by traffic.[9]

During the last decade, more attention has been devoted to the studies on the impact of the surrounding environment on allergies and asthma seeking to elucidate the role of urban green spaces in childhood chronic diseases.[10, 11]

Epidemiologic data on the influence of green spaces on allergy and asthma in children are limited and inconsistent. While some studies have reported an unfavourable influence of green spaces on the prevalence of asthma and the exacerbation of allergic conditions through production of pollen [10, 12] others have reported no relationships between greenery assessed as the Normalized Difference Vegetation Index (NDVI), canopy cover, and asthma.[13, 14] A protective effect of the green environment around homes on the risk of atopic sensitization in children was also founded possible due to increase biodiversity.[15, 16] There is mounting evidence that the close distance from place of residence to city parks and visiting green space has benefits for people's health associated with physical activity, social coherence, and stress-reduction pathways, [17-19] however the evidence of causal relationship between surrounding greenness and asthma in children is inadequate.

Inconsistent associations between green space exposure and childhood asthma have stimulated studies of the relations between the surrounding greenness levels, the distance of the place of residence to city parks, and asthma. This is the first study in Eastern Europe evaluating the long-term impact of quantified greenness levels in the urban environment on the risk of asthma in 4−6 year-old children. In the present study, using individual-level data of a population-based sample and adjusting for important risk factors for asthma, we investigated the associations between objectively estimated residential greenness levels as the NDVI, residential distance to the nearest city park (>1 ha), and the number of children clinically diagnosed with asthma controlling for various covariates. Furthermore, in the stratified analysis we investigated the joint effect-interaction between surrounding greenness, distance to a city park and the risk of asthma in children controlling for PM2.5 and NO2 influence.

MATERIALS AND METHODS

This nested case-control study was conducted as part of the Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe (PHENOTYPE) project funded by the European Commission Seventh Framework Programme.[11] We used Kaunas city pregnant women data that were recruited 2007-2009 to the KANC newborns cohort study. A detailed description of the cohort study has been described previously.[20] In 2012-2013 we invited KANC cohort 3,294 mothers and their 4−6 year's old children to participate in this study. The participants of this research were 1,489 children whose mothers did not change their residence address from the pregnancy, filled in the questionnaires sent by post and agreed to participate in the study. A few missing data were specified by telephone. The study was approved by the Lithuanian Bioethics Committee, and parental informed consent was obtained from all participants. Questionnaire responses by parents or guardians were used to categorise children's basic information, medical history, family history, personal habits, children's height and weight, and housing and environmental conditions. Responses to the standardised International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents were used to identify children with asthma. Childhood asthma was identified by an affirmative response to the question: "Has you child ever had doctor-diagnosed asthma?" Cases (n = 112) were children with clinically diagnosed asthma. Controls (n = 1,377) were children without asthma.

Assessment of exposure to green spaces

Exposure to green spaces was objectively estimated for every child's home addresses using a standardized protocol and assuming that a shorter distance to a city park or a higher NDVI represents a greater exposure to green spaces. In 2012-2013 all children addresses were geocoded to the exact address according to the street name, and house number, and the participants that had lived at their current address since birth at the time the study were included. Kaunas city green space was defined by LANDSAT_5 Thematic Mapper (TM) images at 30 m×30 m resolution retrievals and the NDVI was assigned to individuals' place of residence. The map of the NDVI was generated using the image that was obtained during the maximum vegetation period for our study region − on July 2011. During 2011-2013 years Standardized Precipitation Index (SPI) in Kaunas was optimal and there was no significant yearly variation impacting green space exposure. Mean NDVI values of a straight-line buffer were calculated as estimations of the level of greenness within the immediately accessible neighbourhood (100, 300, and 500 m) of distance every home where various kind of pollen may be expected.

Using the Urban Atlas data for Kaunas city, we estimated the straight-line distance from every participant's home to the nearest city park larger than 1 ha with infrastructure for recreation. In Kaunas only municipality parks greater than 1 ha have infrastructure for recreation and therefore all of them were included in the study. To measure park accessibility the straight-line distance variable is used in most epidemiological studies and is easy to calculate. We constructed binary variable (yes/no) indicating whether the child's residential address was located within 1000 m from a park − having a green space within a 15‑min walk from home, according to the European Commission recommendation.[21]

Most of parks had 65% of the area covered with trees. In the parks and squares 195 species and cultivars of introduced ligneous plants are registered (42 are *Pinophyta*, 153 are *Magnoliophyta*).[22] All the parks are open to the public, without fencing, and have access from all sides, and offer similar recreation opportunities (e.g. walking, jogging, rollerblading, physical training, or resting on the bench) and locations (located among residential homes or establishments), and near public transport lines (5-10 min. by walk) producing good possibility contact of children with environmental biodiversity. To evaluate the possibility that ambient air pollution may confound associations between green spaces and asthma, we used Land Use Regression (LUR) models and modeled a home address-specific measures of fine particulate matter (PM2.5), and ambient concentrations of nitrogen dioxide (NO2). A detailed description of the LUR models has been described previously.[23] During the statistical analysis exposure to PM2.5 and NO2 was categorized by median.

Statistical analysis

We used chi-square and univariate logistic regression analyses to compare the values and frequencies of the baseline characteristics by the studied children's asthma status. Predictor variables whose univariate test showed a statistically significant association (*P*<0.05) with the outcome - or those that changed the adjusted odds ratios (aOR) by 10% or more - were retained for the inclusion in multiple logistic regression analyses. The NDVI, our indicator of residential greenness, was modeled both as a continuous (interquartile range) and categorical (by median) measure. We conducted a sensitivity analyses for asthma outcome. Using logistic regression analysis, we estimated the association between residential greenness in 100, 300, and 500 m buffers by median and interquartile range (IQR) and asthma as crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI). To determine how the associations between residential surrounding greenness and asthma changed based on the distance to parks, the joint effect of the NDVI-100 m (100 m buffer around each maternal home) median and a 1000-meter distance to a park was assessed by including an interaction term in the logistic regression controlling for covariates that may influence the risk of asthma. Odds ratios were adjusted for individual-level mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping cat during the last 12 months, living in a flat, and yearly mean of ambient PM2.5, and NO2. All statistical analyses were performed using SPSS software version 18.0.

RESULTS

Characteristics of the study population

In 2012-2013, we were able to geocode home addresses and estimate residential greenness exposure for 1,489 4−6 year's old children (participants, response rate 45.2%) of 3,294 KANC new-borns cohort who mothers returned questionnaires. The demographic variables of those women who did not respond to the questionnaire (non-participants) were not statistically significantly different from the participants with regard to the birth outcomes and other characteristics (see supplementary file

S1). There was no difference in the residence distance to nearest city park between study participants and non-participants groups. Of the 1,489 study children with complete data, 81.7% had homes located within 1000 meters from the nearest city park (10−15 minutes walking distance) (Figure 1).

The mean surrounding greenness level (NDVI) is presented in Figure 2. The medians (IQR) of the mean NDVI across the buffers of 100, 300, and 500 m around the places of residence were 0.553 (0.110), 0.548 (0.109), and 0.547 (0.116), respectively. The mean annual residential greenness values of the 25th, the 50th, and the 75th percentiles are presented in Table 1. The median (minimum and maximum) of ambient NO2 was 15.85 µg/m3 (8.85−31.05 µg/m3) and PM2.5– 20.44 µg/m3 (15.83–36.09 µg/m3) for residential addresses.

Table 1. Distribution of residential greenness level in different buffers size

Variable	25th	Median	75th	IQR
NDVI-100 m	0.489	0.553	0.599	0.110
NDVI-300 m	0.494	0.548	0.602	0.109
NDVI-500 m	0.491	0.547	0.608	0.116

Physician-diagnosed asthma was reported in 112 (7.5%) children, of whom 91 (81.3%) were living within the 1000-meter buffer zone of the nearest city park.

The descriptive statistics for the characteristics of asthmatic and non-asthmatic children and the prevalence of the investigated variables are presented in Table 2. In general, asthma was more prevalent among 4–6 year-old children whose mothers were less educated, suffered from asthma, were smoking during pregnancy or were exposed to environment tobacco smoke, were living in a flat, or whose children used antibiotics during the first year of life. Children with asthma spent less time in green space than healthy children.

Table 2 Distribution of variables according to children's asthma status

Variables	Asthma yes N (%) (N=112)	Asthma no N (%) (N=1377)
Mother's age at childbirth		
≤30	71 (63.39)	923 (67.03)
31 and more	41 (36.61)	454 (32.97)
Maternal education status		
Low (10 or fewer years)	33 (29.46)*	274 (19.90)
Medium and high (>10 years)	79 (70.54)	1103 (80.10)
Social-economic status		
Low	35 (31.25)	366 (26.58)
Medium, High	77 (68.75)	1011 (73.42)
Maternal smoking during pregnancy		
No	98 (87.50)	1278 (92.81)
Yes	14 (12.50)	99 (7.19)
Maternal passive smoking		
No	66 (58.93)	890 (64.63)
Yes	46 (41.07)	487 (35.37)
Gas cooking		
No	34 (30.36)	501 (36.38)
Yes	78 (69.64)	876 (63.62)
Living in a flat		
No	41 (36.60)	568 (41.25)
Yes	71 (63.40)	809 (58.75)

Sex		
Male	63 (56.25)	675 (49.02)
Female	49 (43.75)	702 (50.98)
Birth order		
1	56 (50.0)	766 (55.62)
2 and more	56 (50.0)	611 (44.38)
Breastfeeding		
No	11 (9.82)	88 (6.39)
Yes	101 (90.18)	1289 (93.61)
Paracetamol use during the first year of life		
No	27 (24.11)	426 (30.94)
Yes	85 (75.89)	951 (69.06)
Antibiotic use during the first year of life		
No	50 (44.64)	924 (67.10)
Yes	62 (55.36)*	453 (32.90)
Asthma in parents		
No	91 (81.25)	1300 (94.41)
Yes	21 (18.75)*	77 (5.59)
Time spent in green space		
≤5 hours	70 (62.50)	753 (54.68)
>5 hours	42 (37.50)	624 (45.32)

* $p<0.05$.

Association between green space and asthma

The proportions of children with asthma had a tendency to increase with an increasing median NDVI in different buffer sizes (Table 3). In addition, the NDVI higher than the median was associated with a 27%, 19%, and 32% increase in the probability of asthma within 100, 300, and 500 m of residences, respectively, in unadjusted models. After adjustment, the associations were similar, yet not statistically significant. The associations of NDVI interquartile range in NDVI-300 m and NDVI-500 m buffer sizes with asthma were similar in magnitude. However, an increase in the interquartile range of green space, using the NDVI-100 m buffer size, was associated with a statistically significant increase in the asthma risk after adjustment for parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, and time spent in green space (aOR 1.43, 95% 1.10−1.85). The distance to a park was not associated with the increased risk of asthma in the unadjusted and adjusted models.

Table 3 Unadjusted and adjusted effects of green spaces as asthma odds ratios (OR) and 95% confidence intervals (CI)

Exposure variables	Asthma yes N (%)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
NDVI-100			
≤median	50 (6.7)	reference	reference
>median	62 (8.4)	1.27 (0.85−1.91)	1.19 (0.79−1.79)
IQR‡		1.43* (1.12−1.82)	1.43* (1.10−1.85)
NDVI-300			
≤median	52 (6.9)	reference	reference
>median	60 (8.1)	1.19 (0.79−1.78)	1.17 (0.78−1.76)
IQR‡		1.21 (0.95−1.56)	1.23 (0.94−1.61)
NDVI-500			
≤median	49 (6.6)	reference	reference

>median	63 (8.5)	1.32 (0.88−1.98)	1.39 (0.92−2.10)
IQR‡		1.15 (0.88−1.50)	1.18 (0.88−1.57)
Distance to a city park			
>1000 m	21 (7.7)	reference	reference
≤1000 m	91 (7.5)	0.97 (0.59−1.59)	0.96 (0.55−1.68)

†Adjusted for: parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, time spent in green space.

‡IQR interquartile range increase.

* $p<0.05$.

Stratified analysis by surrounding greenness and distance to city parks

Seeking to distinguish the effect of greenness level (assessed as NDVI) and park effect and assess their joint effect on the risk of asthma among children we conducted stratified analysis. In this analysis the interaction term included the NDVI-100≤median as a reference, and the distance to a city park − as effect modifier (Table 4). In the sensitivity analysis asthma risk estimates were essentially unchanged after adjustment for maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma**,** maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding**,** living in a flat. After additional adjusting for PM2.5, and NO2, we found the strength of association to be by 15% higher among children residing close to city parks (≤1000 m) in areas with low exposure to green spaces (NDVI-100 m below median); however, the additive park distance effect for an increased risk of asthma was not statistically significant (adjusted OR 1.15, 95% CI 0.50–2.62).

Table 4 The joint effect of NDVI−100 m buffer and distance to a city park on the clinically diagnosed asthma in 4−6 year-old children

100 m buffer NDVI & distance to a city park	Asthma cases No (%)	Unadjusted OR	Adjusted† OR (95% CI)
NDVI-100 ≤median & to city park >1000 m	9 (6.5)	reference	reference
NDVI-100 ≤median & to city park ≤1000 m	41 (6.7)	1.04 (0.47−2.37)	1.15 (0.50−2.62)
NDVI-100 >median & to city park >1000 m	12 (9.0)	1.42 (0.54−3.81)	1.47 (0.56−3.87)
NDVI-100 >median & to city park ≤1000 m	50 (8.2)	1.30 (0.60−2.91)	1.27 (0.56−2.86)

†Adjusted for: maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma**,** maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding**,** living in a flat**,** PM2.5 and NO2.

When comparing the joint effect of NDVI below the median with that above the median within the 100 meter buffer size from home among children with low park exposure (distance to a city park >1000 m), we found that the risk of asthma increased by 47%, and for those living closer to a park, the risk of asthma increased by 27% (adjusted OR 1.27, 95% CI 0.56–2.86). The unadjusted and adjusted results showed that higher greenness levels measured within a 100 meter buffer size of the home had a higher effect on the risk of asthma among 4−6 year-old children than residence closer than 1000 m to a city park did; however, these results were not statistically significant.

DISCUSSION

The results of this nested case-control study present some evidence for the association of the surrounding greenness levels, the distance from the place of residence to city parks, and clinically diagnosed asthma in children. The proportions of children with asthma had a tendency to increase with an increasing median NDVI in different buffer sizes. Regression models adjusted for covariates indicated that an interquartile increase in greenness within 100 m of the surrounding maternal home address was associated with a statistically significant 43% increase in asthma risk at 4–6 years of age; while close residence to a city park was not statistically significant associated with asthma risk.

No individual-level case-control studies are available to compare with this finding; however, these patterns of the associations are similar to the previous reports on the association between greenness and allergies. A cross-sectional study of a population-based sample of 3,178 schoolchildren (9–12 years old) found a higher relative prevalence of current asthma (OR 1.60, 95% CI 1.09−2.36) associated with living within 300 m of parks [13] or higher street tree canopy coverage.[10] However, no statistically significant relationships between the tree canopy coverage and asthma rates were found in a Texas study.[14] Previously, in an ecological-design study, an inverse association was observed between an increase in street tree density and a decrease in the prevalence of asthma among children in urban areas such as New York City,[15] yet this does not permit an inference that trees are causally related to the prevalence of asthma at the individual level.

The difference in study design and greenness (tree species and park plant biodiversity) may have an impact on the observed different levels of associations between residential distance to forests and to parks and the prevalence of childhood asthma.[13, 24] Also, a difference between forest and park flora and the composition of ambient pollen concentrations could explain these variations.[10, 12, 25] A clinical study in Korea showed that short-term exposure to forest environment may have positive clinical and immunological effects in children with allergic diseases who were living in the urban community.[26] Furthermore, residential location, social factors, age, and education are likely to have an impact on the use of green spaces and the course of allergic diseases.[27, 28] A cohort study in Germany found area-specific heterogeneous associations across urban and rural study areas between mean greenness in a 500 m buffer around the home address at 10 years and childhood allergies: positively associated with allergic rhinitis and eyes and nose symptoms in the urban area and negatively associated in rural area.[29]

There is some evidence of the children health benefits associated with outdoor activities and time spent in a natural environment such as a park or other recreational area. By reducing noise and transport-related air pollution levels, enhancing physical activity, and minimizing sedentary life style, greenness may have a positive impact on the reduction of psychophysiological stress in children residing in poorer housing and environmental conditions.[30-32]

Some of our observed associations between higher residential greenness levels and an increased risk of asthma are consistent with the results of the previous studies, while others are not. In a New York city cohort study, asthma among 7 year-old children increased by 17% per standard deviation increase of tree canopy coverage (adjusted risk ratios 1.17, 95% CI 1.02–1.33).[14] The results of this study are in line with those of the previous studies, suggesting that high exposure to green spaces may increase the risk of allergic conditions and the prevalence of asthma through the production of pollen.[10, 12] On the other hand, the decrease in the biodiversity of the living environment has been associated with dysfunctions of the immune system and increasing allergies.[24, 33] A cross-sectional study of schoolchildren in Sabadell, Spain, concluded that an interquartile range increase in residential surrounding greenness across 100 m buffer around participants' home addresses was not associated with current asthma (OR 1.00, 95% CI 0.82–1.21).[13] No statistically significant relationships between NDVI and the prevalence of asthma were found in an ecological study, which did not control for possible confounding covariates.[14] However, cohorts from Finland and Estonia reported that the amount of green environment around homes was inversely associated with the risk of atopic sensitization in children 6 years of age and older.[16] The authors concluded that environmental biodiversity affects the composition of the human skin microbiota, influences immune tolerance, and decreases the risk of atopic sensitization in children.

We found stronger associations for asthma among children exposed to higher surrounding greenness than for those living close to city parks, nevertheless that child with asthma spent less time in green space than healthy children. These associations did not change after adjusting for other individual and environment variables, including ambient PM2.5 and NO2 suggesting that residential greenness have impact on children asthma prevalence. However, we should to account the findings that visits to green space has positive effect on children health through psychophysiological stress reduction and increased physical activity, nevertheless that there is no clear understanding mechanisms of the impact of the exposure to green spaces on allergy and asthma in children.[11, 34] Heterogeneous associations of residential greenness with allergic conditions further emphasize that the effect of green spaces on health is complex and needs to be further investigated across studies that vary in the composition of green spaces, air quality, and population groups.

Our study faced some limitations. In this study, the use of one NDVI image may produce green space exposure measurement error; assuming this error is non-differential for asthmatic and non-asthmatic children but it might attenuate long-term exposure effect estimates. However, our study used the same research conditions and objective environmental measurements, including individual yearly mean air pollutants exposure. Measurement errors also may be present in the evaluation of health outcomes, and the estimations of the associations may be skewed by unmeasured confounding data obtained by parents' responses to questions on their children's asthma, as well as by variables that could have resulted in the misclassification of health outcomes and might have attenuated the strengths of the observed associations. However, this limitation is assumed to be random. The results are also affected by the small sample sizes albeit large enough to detect some significant effects. However, small sample sizes used in the stratified analysis may have an impact on the ability to detect a statistically significant relationship.

The current study had the advantage of using a large number of covariates gathered during the interview, and thus may individually control for covariates associated with asthma, such as smoking, maternal diseases, education, and others. Another advantage is the objective estimation of exposure to green spaces and major ambient air pollutants at the individual level and the possibility to avoid exposure misclassification associated with participants' mobility. Even though many covariates in the analyses were considered, residual confounding remains possible. Antenatal allergic sensitization, which is the most common precursor to the development of asthma and polymorphisms in inflammation genes might affect the association between environmental exposures and the risk of asthma in early childhood.[7, 35] Additional associations that may be considered in the future research include chronic stress in children and the interaction between the behavioural, genetic, and environmental risk factors that may be related to asthma. The generalizability of our findings may, however, be somewhat limited since possible differences in surrounding greenness exposure and park biodiversity.

CONCLUSIONS

This study demonstrates positive associations between surrounding greenness quantity within the buffer of 100 m from each child's home and the prevalence of asthma among 4–6 year-old children, and this association persists after adjusting for individual-level covariates and exposures to air pollution. Although findings in the stratified analyses on the joint effect of the surrounding greenness and the distance to city parks lack of statistical significance and require further confirmation by other studies, they highlight the need for more research on the effect of the natural environment on children's health. Equivocal and inconsistent results from previous epidemiologic studies on green space exposure effects on asthma may be attributable to the crude exposure assessment that did not adequately represent the individual exposure, differences in subgroups susceptibility or health behaviour. Future investigation of causal relationship between surrounding greenness and childhood asthma could provide preventive measures for allergy management and intervention programs, particularly of behavioral change, and stress management.

CONTRIBUTORSHIP STATEMENT SA performed statistical analysis, drafted of the methods, and was the lead writer. RG conceived the idea, designed the study, and revised of the manuscript. JK assisted with the writing of the manuscript and revised the manuscript. AB assisted with the writing and revising of the manuscript. AD modelled air pollution data, created GIS maps, and revised the manuscript. MJN conceptualised and supervised the analyses, and critically reviewed the manuscript. All authors critically reviewed and revised the manuscript, and approved the final version of the manuscript as submitted.

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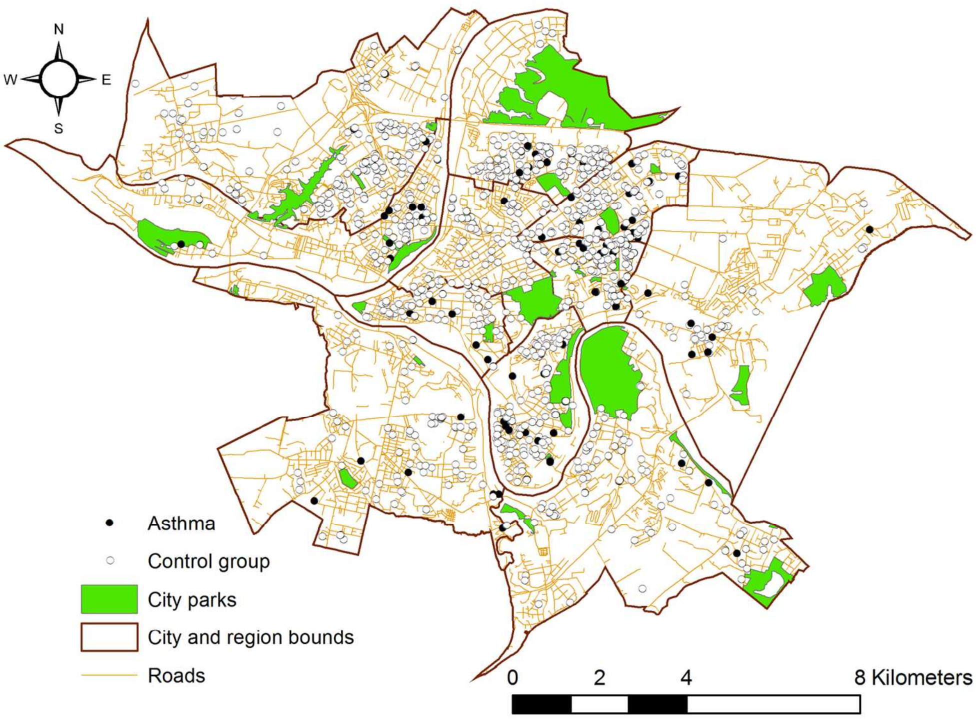

Figure 1 Spatial distribution of study population (asthma cases and controls), neighbourhood walkability and Kaunas city parks locations.
146x109mm (300 x 300 DPI)

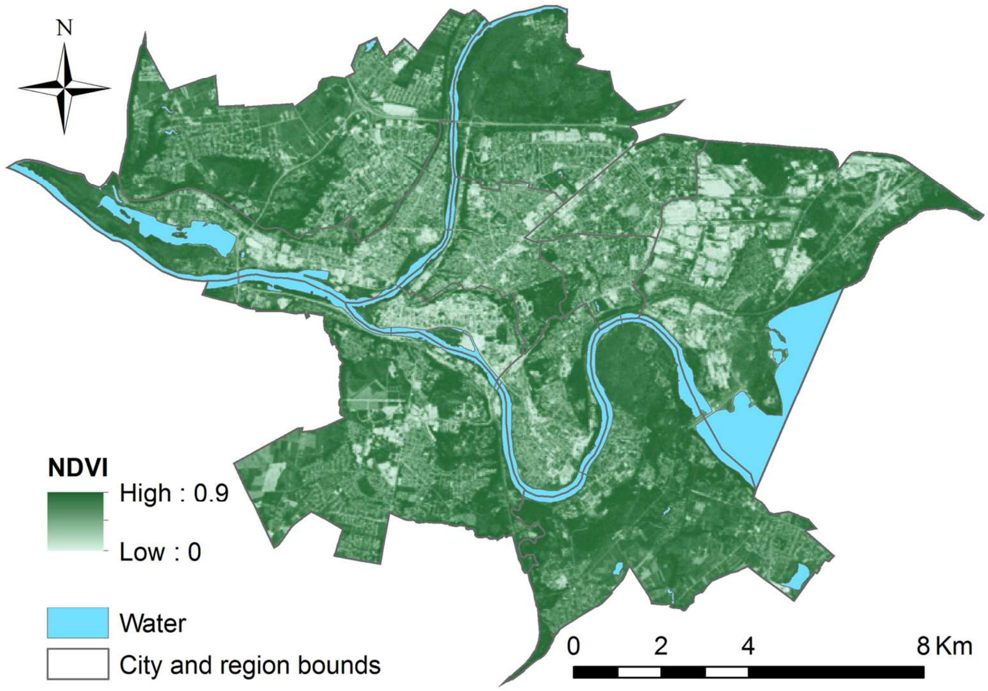

Figure 2 Spatial distribution of greenness level for the Kaunas city measured with satellite-derived NDVI.
143x106mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Within title page 1 and page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 3-4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 2 and 4]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Methods pages 4-5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[pages 4-5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[page 5]**
		(*b*) For matched studies, give matching criteria and the number of controls per case **[NA]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 5-6]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 5-6]**
Bias	9	Describe any efforts to address potential sources of bias **[page 7]**
Study size	10	Explain how the study size was arrived at **[page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[pages 5-7]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[page 7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[page 7]**
		(*c*) Explain how missing data were addressed **[7, S1]**
		(*d*) If applicable, explain how matching of cases and controls was addressed **[NA]**
		(*e*) Describe any sensitivity analyses [**page 7]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 7-8, S1]**
		(b) Give reasons for non-participation at each stage **[NA]**
		(c) Consider use of a flow diagram [NA]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[pages 8-9, tables 1, 2]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure **[page 8, table 1, figures 1, 2]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[pages 10-13, tables 3, 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[page 9]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[pages 10-13, Tables 3, 4]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[page 13-16]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[page 16]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[page 16]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[pages 17-18]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 18]**

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

S1. Distribution of the main characteristics study participants and non-participants.

Characteristic	Participants % (N=1489)	Non-participants % (N=1805)	p-value
Maternal age at childbirth			
≤ 30 year	56.6	59.5	p=0.21
>30 year	43.4	40.5	
Marital status			
Married	87.5	84.9	p=0.11
Not married	12.5	15.1	
Socio-economic status			
Low	30.3	32.2	p=0.61
Medium	54.9	52.6	
High	14.8	15.2	
Maternal smoking during pregnancy			
No	95.3	95.7	p=0.68
Yes	4.7	4.3	
Maternal passive smoking			
No	56.4	52.1	p=0.06
Yes	43.6	47.9	
Low birth weight newborn (<2500 g)			
No	95.3	95.5	p=0.82
Yes	4.7	4.5	
Preterm birth (<37 weeks)			
No	94.9	94.2	p=0.55
Yes	5.1	5.8	

Distance to city park (m)			
≤ 300	26.6	25.0	p=0.74
300-999	60.2	61.4	
≥1000	13.2	13.6	

Associations between Neighbourhood Greenness and Asthma in Preschool Children in Kaunas, Lithuania: a Case-control Study

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Associations between Neighbourhood Greenness and Asthma in Preschool Children in Kaunas, Lithuania: a Case-control Study

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ABSTRACT

Objectives: The aim of this study was to investigate the associations between surrounding greenness levels and asthma among children, and to explore possible change of this association by the distance of the residence to a city park.

Design: A nested case-control study.

Setting: Children of 4−6 year's age residing at their current address since birth in Kaunas, Lithuania, whose mothers were recruited 2007-2009 to the KANC newborns cohort study.

Participants: 1,489 children whose parents in 2012-2013 filled in the questionnaires and agreed to participate in the study.

Primary and secondary outcome measures: We estimated clinically diagnosed asthma risk factors. The surrounding greenness was measured as the average of the satellite-based Normalized Difference Vegetation Index (NDVI) within the buffers of 100, 300, and 500 m from each child's home address, and the distance to a city park was defined as the distance to the nearest city park. Multivariate logistic regression was performed to study the relationship between the greenness exposures and asthma adjusted for relevant covariates.

Results. An increase in the NDVI (>median) in buffers of 100, 300, and 500 m was associated with a slightly increased risk of asthma, while an interquartile range increase in NDVI-100 m statistically significant increased the risk of asthma (OR 1.43, 95% CI 1.10−1.85). The stratified analysis by surrounding greenness revealed indications of stronger associations for children with higher surrounding greenness (NDVI-100>median) and those living farther away from parks (>1000 m), compared to NDVI-100≤median and the distance to a city park >1000 m (OR 1.47, 95% CI 0.56−3.87*)*.

Conclusions. Higher level of the surrounding greenness was associated with a slightly increased relative risk of asthma in children. Further investigation is needed to elucidate the influence of city parks and neighbourhood greenness levels on asthma.

Keywords: Child asthma, green spaces, city park, quantified greenness levels.

STRENGTHS AND LIMITATIONS OF THIS STUDY

•The current nested case-control study had the advantage of using a large number of covariates gathered during the interview, and the objective individual-level estimation of exposure to green spaces buffers around the home addresses and major ambient air pollutants.

•This is the first case-control study demonstrating the positive associations between greater quantity of greenness in the 100 m buffer size of home, assessed at an individual level, and the increased risk of asthma in children of 4−6 year's age residing at their current address since birth.

•The analysis of the joint effect of surrounding greenness and distance to park on asthma risk controlling for relevant covariates and fine particulate matter (PM2.5), and ambient concentrations of nitrogen dioxide (NO2) showed a slight additive effect on the strength of association; therefore, further investigations are needed to confirm this nested case-control study results.

INTRODUCTION

Asthma is the most prevalent chronic disease among children. Over the last decades, the prevalence of asthma has progressively increased in the industrialized world and in developing regions.[1, 2] There is large geographical variation in the prevalence of asthma ranging from less than 2% to more than 20% in some countries.[3, 4] The majority of the causative agents of asthma in children remains uncertain and need clarification. Asthma likely depends on a number of interacting factors, including genetic, behavioural and environmental risk factors,[5-8] including long-term exposure to urban air pollutants emitted by traffic.[9]

During the last decade, more attention has been devoted to the studies on the impact of the surrounding environment on allergies and asthma seeking to elucidate the role of urban green spaces in childhood chronic diseases.[10, 11]

Epidemiologic data on the influence of green spaces on allergy and asthma in children are limited and inconsistent. While some studies have reported an unfavourable influence of green spaces on the prevalence of asthma and the exacerbation of allergic conditions through production of pollen [10, 12] others have reported no relationships between greenery assessed as the Normalized Difference Vegetation Index (NDVI), canopy cover, and asthma.[13, 14] A protective effect of the green environment around homes on the risk of atopic sensitization in children was also founded possible due to increase biodiversity.[15, 16] There is mounting evidence that the close distance from place of residence to city parks and visiting green space has benefits for people's health associated with physical activity, social coherence, and stress-reduction pathways,[17-19] however the evidence of causal relationship between surrounding greenness and asthma in children is inadequate.

Inconsistent associations between green space exposure and childhood asthma have stimulated studies of the relations between the surrounding greenness levels, the distance of the place of residence to city parks, and asthma. This is the first study in Eastern Europe evaluating the long-term impact of quantified greenness levels in the urban environment on the risk of asthma in 4−6 year-old children. In the present study, using individual-level data of a population-based sample and adjusting for important risk factors for asthma, we investigated the associations between objectively estimated residential greenness levels as the NDVI, residential distance to the nearest city park (>1 ha), and the number of children clinically diagnosed with asthma controlling for various covariates. Furthermore, in the stratified analysis we investigated the joint effect-interaction between surrounding greenness, distance to a city park and the risk of asthma in children controlling for PM2.5 and NO2 influence.

MATERIALS AND METHODS

This nested case-control study was conducted as part of the Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe (PHENOTYPE) project funded by the European Commission Seventh Framework Programme.[11] We used Kaunas city pregnant women data that were recruited 2007-2009 to the KANC newborns cohort study. A detailed description of the cohort study has been described previously.[20] In 2012-2013 we invited KANC cohort 3,294 mothers and their 4−6 year's old children to participate in this study. The participants of this research were 1,489 children whose mothers did not change their residence address from the pregnancy, filled in the questionnaires sent by post and agreed to participate in the study. A few missing data were specified by telephone. The study was approved by the Lithuanian Bioethics Committee, and parental informed consent was obtained from all participants.

Questionnaire responses by parents or guardians were used to categorise children's basic information, medical history, family history, personal habits, children's height and weight, and housing and environmental conditions. Responses to the standardised International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents were used to identify children with asthma. Childhood asthma was identified by an affirmative response to the question: "Has you child ever had doctor-diagnosed asthma?" Cases (n = 112) were children with clinically diagnosed asthma. Controls (n = 1,377) were children without asthma.

Assessment of exposure to green spaces

Exposure to green spaces was objectively estimated for every child's home addresses using a standardized protocol and assuming that a shorter distance to a city park or a higher NDVI represents a greater exposure to green spaces. In 2012-2013 all children addresses were geocoded to the exact address according to the street name, and house number, and the participants that had lived at their current address since birth at the time the study were included. Kaunas city green space was defined by LANDSAT_5 Thematic Mapper (TM) images at 30 m×30 m resolution retrievals and the NDVI was assigned to individuals' place of residence. The map of the NDVI was generated using the image that was obtained during the maximum vegetation period for our study region − on July 2011. During 2011-2013 years Standardized Precipitation Index (SPI) in Kaunas was optimal and there was no significant yearly variation impacting green space exposure. Mean NDVI values of a straight-line buffer were calculated as estimations of the level of greenness within the immediately accessible neighbourhood (100, 300, and 500 m) of distance every home where various kind of pollen may be expected.

Using the Urban Atlas data for Kaunas city, we estimated the straight-line distance from every participant's home to the nearest city park larger than 1 ha with infrastructure for recreation. In Kaunas only municipality parks greater than 1 ha have infrastructure for recreation and therefore all of them were included in the study. To measure park accessibility the straight-line distance variable was suggested to use in PHENOTYPE epidemiological studies seeking to receive comparable results and is easy to calculate. We constructed binary variable (yes/no) indicating whether the child's residential address was located within 1000 m from a park − having a green space within a 15‑min walk from home, according to the European Commission recommendation.[21]

Most of parks had 65% of the area covered with trees. In the parks and squares 195 species and cultivars of introduced ligneous plants are registered (42 are *Pinophyta*, 153 are *Magnoliophyta*).[22] All the parks are open to the public, without fencing, and have access from all sides, and offer similar recreation opportunities (e.g. walking, jogging, rollerblading, physical training, or resting on the bench) and locations (located among residential homes or establishments), and near public transport lines (5-10 min. by walk) producing good possibility contact of children with environmental biodiversity. To evaluate the possibility that ambient air pollution may confound associations between green spaces and asthma, we used Land Use Regression (LUR) models and modeled a home address-specific measures of fine particulate matter (PM2.5), and ambient concentrations of nitrogen dioxide (NO2). A detailed description of the LUR models has been described previously.[23] During the statistical analysis exposure to PM2.5 and NO2 was categorized by median.

Statistical analysis

We used chi-square and univariate logistic regression analyses to compare the values and frequencies of the baseline characteristics by the studied children's asthma status. Predictor variables whose univariate test showed a statistically significant association (P<0.05) with the outcome - or those that changed the adjusted odds ratios (aOR) by 10% or more - were retained for the inclusion in multiple logistic regression analyses. The NDVI, our indicator of residential greenness, was modeled both as a continuous (interquartile range) and categorical (by median) measure. We conducted a sensitivity analyses for asthma outcome. Using logistic regression analysis, we estimated the association between residential greenness in 100, 300, and 500 m buffers by median and interquartile range (IQR) and asthma as crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI). To determine how the associations between residential surrounding greenness and asthma changed based on the distance to parks, the joint effect of the NDVI-100 m (100 m buffer around each maternal home) median and a 1000-meter distance to a park was assessed by including an interaction term in the logistic regression controlling for covariates that may influence the risk of asthma. Odds ratios were adjusted for individual-level mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping cat during the last 12 months, living in a flat, and yearly mean of ambient PM2.5, and NO2. All statistical analyses were performed using SPSS software version 18.0.

RESULTS

Characteristics of the study population

In 2012-2013, we were able to geocode home addresses and estimate residential greenness exposure for 1,489 4−6 year's old children (participants, response rate 45.2%) of 3,294 KANC new-borns cohort who mothers returned questionnaires. The demographic variables of those women who did not respond to the questionnaire (non-participants) were not statistically significantly different from the participants with regard to the birth outcomes and other characteristics (see supplementary file

S1). There was no difference in the residence distance to nearest city park between study participants and non-participants groups. Of the 1,489 study children with complete data, 81.7% had homes located within 1000 meters from the nearest city park (10−15 minutes walking distance) (Figure 1).

The mean surrounding greenness level (NDVI) is presented in Figure 2. The medians (IQR) of the mean NDVI across the buffers of 100, 300, and 500 m around the places of residence were 0.553 (0.110), 0.548 (0.109), and 0.547 (0.116), respectively. The mean annual residential greenness values of the 25th, the 50th, and the 75th percentiles are presented in Table 1. The median (minimum and maximum) of ambient NO2 was 15.85 μg/m3 (8.85−31.05 μg/m3) and PM2.5– 20.44 μg/m3 (15.83–36.09 μg/m3) for residential addresses.

Table 1. Distribution of residential greenness level in different buffers size

Variable	25th	Median	75th	IQR
NDVI-100 m	0.489	0.553	0.599	0.110
NDVI-300 m	0.494	0.548	0.602	0.109
NDVI-500 m	0.491	0.547	0.608	0.116

Physician-diagnosed asthma was reported in 112 (7.5%) children, of whom 91 (81.3%) were living within the 1000-meter buffer zone of the nearest city park.

The descriptive statistics for the characteristics of asthmatic and non-asthmatic children and the prevalence of the investigated variables are presented in Table 2. In general, asthma was more prevalent among 4–6 year-old children whose mothers were less educated, suffered from asthma, were smoking during pregnancy or were exposed to environment tobacco smoke, were living in a flat, or whose children used antibiotics during the first year of life. Children with asthma spent less time in green space than healthy children.

Table 2 Distribution of variables according to children's asthma status

Variables	Asthma yes N (%) (N=112)	Asthma no N (%) (N=1377)
Mother's age at childbirth		
≤30	71 (63.39)	923 (67.03)
31 and more	41 (36.61)	454 (32.97)
Maternal education status		
Low (10 or fewer years)	33 (29.46)*	274 (19.90)
Medium and high (>10 years)	79 (70.54)	1103 (80.10)
Social-economic status		
Low	35 (31.25)	366 (26.58)
Medium, High	77 (68.75)	1011 (73.42)
Maternal smoking during pregnancy		
No	98 (87.50)	1278 (92.81)
Yes	14 (12.50)	99 (7.19)
Maternal passive smoking		
No	66 (58.93)	890 (64.63)
Yes	46 (41.07)	487 (35.37)
Gas cooking		
No	34 (30.36)	501 (36.38)
Yes	78 (69.64)	876 (63.62)
Living in a flat		
No	41 (36.60)	568 (41.25)
Yes	71 (63.40)	809 (58.75)

Sex		
Male	63 (56.25)	675 (49.02)
Female	49 (43.75)	702 (50.98)
Birth order		
1	56 (50.0)	766 (55.62)
2 and more	56 (50.0)	611 (44.38)
Breastfeeding		
No	11 (9.82)	88 (6.39)
Yes	101 (90.18)	1289 (93.61)
Paracetamol use during the first year of life		
No	27 (24.11)	426 (30.94)
Yes	85 (75.89)	951 (69.06)
Antibiotic use during the first year of life		
No	50 (44.64)	924 (67.10)
Yes	62 (55.36)*	453 (32.90)
Asthma in parents		
No	91 (81.25)	1300 (94.41)
Yes	21 (18.75)*	77 (5.59)
Time spent in green space		
≤5 hours	70 (62.50)	753 (54.68)
>5 hours	42 (37.50)	624 (45.32)

* $p<0.05$.

Association between green space and asthma

The proportions of children with asthma had a tendency to increase with an increasing median NDVI in different buffer sizes (Table 3). In addition, the NDVI higher than the median was associated with a 27%, 19%, and 32% increase in the probability of asthma within 100, 300, and 500 m of residences, respectively, in unadjusted models. After adjustment, the associations were similar, yet not statistically significant. The associations of NDVI interquartile range in NDVI-300 m and NDVI-500 m buffer sizes with asthma were similar in magnitude. However, an increase in the interquartile range of green space, using the NDVI-100 m buffer size, was associated with a statistically significant increase in the asthma risk after adjustment for parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, and time spent in green space (aOR 1.43, 95% 1.10−1.85). The distance to a park was not associated with the increased risk of asthma in the unadjusted and adjusted models.

Table 3 Unadjusted and adjusted effects of green spaces as asthma odds ratios (OR) and 95% confidence intervals (CI)

Exposure variables	Asthma yes N (%)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
NDVI-100			
≤median	50 (6.7)	reference	reference
>median	62 (8.4)	1.27 (0.85−1.91)	1.19 (0.79−1.79)
IQR‡		1.43* (1.12−1.82)	1.43* (1.10−1.85)
NDVI-300			
≤median	52 (6.9)	reference	reference
>median	60 (8.1)	1.19 (0.79−1.78)	1.17 (0.78−1.76)
IQR‡		1.21 (0.95−1.56)	1.23 (0.94−1.61)
NDVI-500			
≤median	49 (6.6)	reference	reference

>median	63 (8.5)	1.32 (0.88−1.98)	1.39 (0.92−2.10)
IQR‡		1.15 (0.88−1.50)	1.18 (0.88−1.57)
Distance to a city park			
>1000 m	21 (7.7)	reference	reference
≤1000 m	91 (7.5)	0.97 (0.59−1.59)	0.96 (0.55−1.68)

†Adjusted for: parental asthma, maternal education, age at childbirth, smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the last 12 months, living in a flat, time spent in green space.

‡IQR interquartile range increase.

* $p<0.05$.

Stratified analysis by surrounding greenness and distance to city parks

Seeking to distinguish the effect of greenness level (assessed as NDVI) and park effect and assess their joint effect on the risk of asthma among children we conducted stratified analysis. In this analysis the interaction term included the NDVI-100≤median as a reference, and the distance to a city park − as effect modifier (Table 4). In the sensitivity analysis asthma risk estimates were essentially unchanged after adjustment for maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma**,** maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding**,** living in a flat. After additional adjusting for PM2.5, and NO2, we found the strength of association to be by 15% higher among children residing close to city parks (≤1000 m) in areas with low exposure to green spaces (NDVI-100 m below median); however, the additive park distance effect for an increased risk of asthma was not statistically significant (adjusted OR 1.15, 95% CI 0.50–2.62).

Table 4 The joint effect of NDVI−100 m buffer and distance to a city park on the clinically diagnosed asthma in 4−6 year-old children

100 m buffer NDVI & distance to a city park	Asthma cases No (%)	Unadjusted OR	Adjusted† OR (95% CI)
NDVI-100 ≤median & to city park >1000 m	9 (6.5)	reference	reference
NDVI-100 ≤median & to city park ≤1000 m	41 (6.7)	1.04 (0.47−2.37)	1.15 (0.50−2.62)
NDVI-100 >median & to city park >1000 m	12 (9.0)	1.42 (0.54−3.81)	1.47 (0.56−3.87)
NDVI-100 >median & to city park ≤1000 m	50 (8.2)	1.30 (0.60−2.91)	1.27 (0.56−2.86)

†Adjusted for: maternal smoking during pregnancy, antibiotic use during the first year of life, parental asthma**,** maternal education, mother's age at childbirth, keeping cat during the last 12 months, breastfeeding**,** living in a flat**,** PM2.5 and NO2.

When comparing the joint effect of NDVI below the median with that above the median within the 100 meter buffer size from home among children with low park exposure (distance to a city park >1000 m), we found that the risk of asthma increased by 47%, and for those living closer to a park, the risk of asthma increased by 27% (adjusted OR 1.27, 95% CI 0.56–2.86). The unadjusted and adjusted results showed that higher greenness levels measured within a 100 meter buffer size of the home had a higher effect on the risk of asthma among 4−6 year-old children than residence closer than 1000 m to a city park did; however, these results were not statistically significant.

DISCUSSION

The results of this nested case-control study present some evidence for the association of the surrounding greenness levels, the distance from the place of residence to city parks, and clinically diagnosed asthma in children. The proportions of children with asthma had a tendency to increase with an increasing median NDVI in different buffer sizes. Regression models adjusted for covariates indicated that an interquartile increase in greenness within 100 m of the surrounding maternal home address was associated with a statistically significant 43% increase in asthma risk at 4–6 years of age; while close residence to a city park was not statistically significant associated with asthma risk.

No individual-level case-control studies are available to compare with this finding; however, these patterns of the associations are similar to the previous reports on the association between greenness and allergies. A cross-sectional study of a population-based sample of 3,178 schoolchildren (9–12 years old) found a higher relative prevalence of current asthma (OR 1.60, 95% CI 1.09−2.36) associated with living within 300 m of parks [13] or higher street tree canopy coverage.[10] However, no statistically significant relationships between the tree canopy coverage and asthma rates were found in a Texas study.[14] Previously, in an ecological-design study, an inverse association was observed between an increase in street tree density and a decrease in the prevalence of asthma among children in urban areas such as New York City,[15] yet this does not permit an inference that trees are causally related to the prevalence of asthma at the individual level.

The difference in study design and greenness (tree species and park plant biodiversity) may have an impact on the observed different levels of associations between residential distance to forests and to parks and the prevalence of childhood asthma.[13, 24] Also, a difference between forest and park flora and the composition of ambient pollen concentrations could explain these variations.[10, 12, 25] A clinical study in Korea showed that short-term exposure to forest environment may have positive clinical and immunological effects in children with allergic diseases who were living in the urban community.[26] Furthermore, residential location, social factors, age, and education are likely to have an impact on the use of green spaces and the course of allergic diseases.[27, 28] A cohort study in Germany found area-specific heterogeneous associations across urban and rural study areas between mean greenness in a 500 m buffer around the home address at 10 years and childhood allergies: positively associated with allergic rhinitis and eyes and nose symptoms in the urban area and negatively associated in rural area.[29]

There is some evidence of the children health benefits associated with outdoor activities and time spent in a natural environment such as a park or other recreational area. By reducing noise and transport-related air pollution levels, enhancing physical activity, and minimizing sedentary life style, greenness may have a positive impact on the reduction of psychophysiological stress in children residing in poorer housing and environmental conditions.[30-32]

Some of our observed associations between higher residential greenness levels and an increased risk of asthma are consistent with the results of the previous studies, while others are not. In a New York city cohort study, asthma among 7 year-old children increased by 17% per standard deviation increase of tree canopy coverage (adjusted risk ratios 1.17, 95% CI 1.02–1.33).[14] The results of this study are in line with those of the previous studies, suggesting that high exposure to green spaces may increase the risk of allergic conditions and the prevalence of asthma through the production of pollen.[10, 12] On the other hand, the decrease in the biodiversity of the living environment has been associated with dysfunctions of the immune system and increasing allergies.[24, 33] A cross-sectional study of schoolchildren in Sabadell, Spain, concluded that an interquartile range increase in residential surrounding greenness across 100 m buffer around participants' home addresses was not associated with current asthma (OR 1.00, 95% CI 0.82–1.21).[13] No statistically significant relationships between NDVI and the prevalence of asthma were found in an ecological study, which did not control for possible confounding covariates.[14] However, cohorts from Finland and Estonia reported that the amount of green environment around homes was inversely associated with the risk of atopic sensitization in children 6 years of age and older.[16] The authors concluded that environmental biodiversity affects the composition of the human skin microbiota, influences immune tolerance, and decreases the risk of atopic sensitization in children.

We found stronger associations for asthma among children exposed to higher surrounding greenness than for those living close to city parks, nevertheless that child with asthma spent less time in green space than healthy children. These associations did not change after adjusting for other individual and environment variables, including ambient PM2.5 and NO2 suggesting that residential greenness have impact on children asthma prevalence. However, we should to account the findings that visits to green space has positive effect on children health through psychophysiological stress reduction and increased physical activity, nevertheless that there is no clear understanding mechanisms of the impact of the exposure to green spaces on allergy and asthma in children.[11, 34] The underlying mechanisms for positive surrounding greenness impact on children health may be partially explained by the physiological study's findings of healthy subjects, indicating that walking in the forest environment can facilitate homeostasis through positive effects on the central and autonomic nervous system, and endocrine system [35, 36]. In addition, immunology research shows that green spaces can increase human immune function by facilitating the activity of macrophage cells [37]. Children with poorly controlled asthma, chronic airways inflammation and episodic respiratory symptoms have dysfunctional alveolar macrophage phagocytic immune response [38, 39] therefore green space through facilitate homeostasis may have different effect. Heterogeneous associations of residential greenness with allergic conditions further emphasize that the effect of green spaces on health is complex and needs to be further investigated across studies that vary in the composition of green spaces, air quality, and population groups.

Our study faced some limitations. In this study, the use of one NDVI image and straight-line distance rather than the road network for park accessibility may produce green space exposure measurement error; assuming this error is non-differential for asthmatic and non-asthmatic children but it might attenuate long-term exposure effect estimates. However, our study used the same research conditions and objective environmental measurements, including individual yearly mean air pollutants exposure. Measurement errors also may be present in the evaluation of health outcomes, and the estimations of the associations may be skewed by unmeasured confounding data obtained by parents' responses to questions on their children's asthma, as well as by variables that could have resulted in the misclassification of health outcomes and might have attenuated the strengths of the observed associations. However, this limitation is assumed to be random. The results are also affected by the small sample sizes albeit large enough to detect some significant effects. However, small sample sizes used in the stratified analysis may have an impact on the ability to detect a statistically significant relationship.

The current study had the advantage of using a large number of covariates gathered during the interview, and thus may individually control for covariates associated with asthma, such as smoking, maternal diseases, education, and others. Another advantage is the objective estimation of exposure to green spaces and major ambient air pollutants at the individual level and the possibility to avoid exposure misclassification associated with participants' mobility. Even though many covariates in the analyses were considered, residual confounding remains possible. Antenatal allergic sensitization, which is the most common precursor to the development of asthma and polymorphisms in inflammation genes might affect the association between environmental exposures and the risk of asthma in early childhood.[7, 40] Additional associations that may be considered in the future research include chronic stress in children and the interaction between the behavioural, genetic, and environmental risk factors that may be related to asthma. The generalizability of our findings may, however, be somewhat limited since possible differences in surrounding greenness exposure and park biodiversity.

CONCLUSIONS

This study demonstrates positive associations between surrounding greenness quantity within the buffer of 100 m from each child's home and the prevalence of asthma among 4–6 year-old children, and this association persists after adjusting for individual-level covariates and exposures to air pollution. Although findings in the stratified analyses on the joint effect of the surrounding greenness and the distance to city parks lack of statistical significance and require further confirmation by other studies, they highlight the need for more research on the effect of the natural environment on children's health. Equivocal and inconsistent results from previous epidemiologic studies on green space exposure effects on asthma may be attributable to the crude exposure assessment that did not adequately represent the individual exposure, differences in subgroups susceptibility or health behaviour. Future investigation of causal relationship between surrounding greenness and childhood asthma could provide preventive measures for allergy management and intervention programs, particularly of behavioral change, and stress management.

CONTRIBUTORSHIP STATEMENT SA performed statistical analysis, drafted of the methods, and was the lead writer. RG conceived the idea, designed the study, and revised of the manuscript. JK assisted with the writing of the manuscript and revised the manuscript. AB assisted with the writing and revising of the manuscript. AD modelled air pollution data, created GIS maps, and revised the manuscript. MJN conceptualised and supervised the analyses, and critically reviewed the manuscript. All authors critically reviewed and revised the manuscript, and approved the final version of the manuscript as submitted.

COMPETING INTERESTS None.

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DATA SHARING STATEMENT No additional data are available.

PATIENTS CONSENT Obtained from parents.

ETHICS APPROVAL This study was approved by the Lithuanian Bioethics Committee.

PROVENANCE ANP PEER REVIEW Not commissioned; externally peer reviewed.

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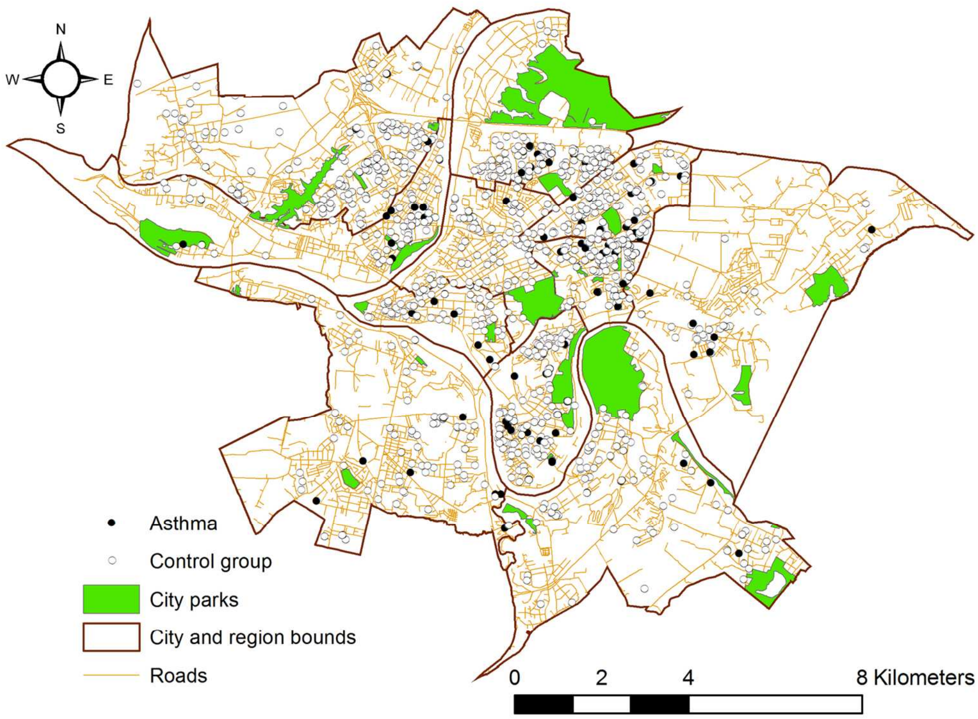
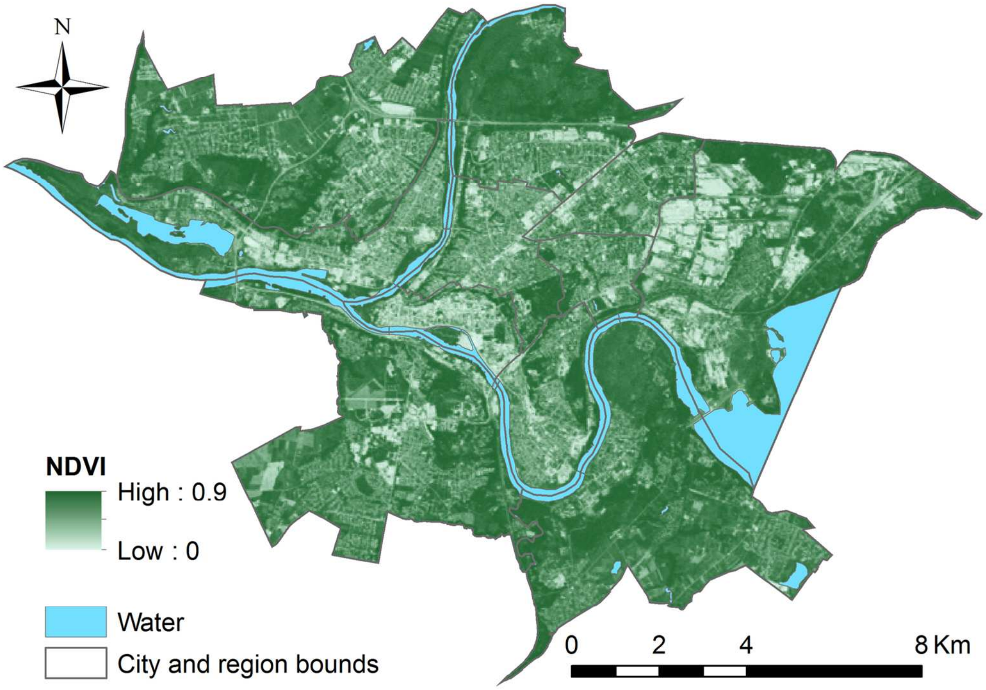


Spatial distribution of study population (asthma cases and controls), neighbourhood walkability and Kaunas city parks locations.
146x109mm (300 x 300 DPI)



Spatial distribution of greenness level for the Kaunas city measured with satellite-derived NDVI.
143x106mm (300 x 300 DPI)

S1. Distribution of the main characteristics study participants and non-participants.

Characteristic	Participants % (N=1489)	Non-participants % (N=1805)	p-value
Maternal age at childbirth			
≤ 30 year	56.6	59.5	p=0.21
>30 year	43.4	40.5	
Marital status			
Married	87.5	84.9	p=0.11
Not married	12.5	15.1	
Socio-economic status			
Low	30.3	32.2	p=0.61
Medium	54.9	52.6	
High	14.8	15.2	
Maternal smoking during pregnancy			
No	95.3	95.7	p=0.68
Yes	4.7	4.3	
Maternal passive smoking			
No	56.4	52.1	p=0.06
Yes	43.6	47.9	
Low birth weight newborn (<2500 g)			
No	95.3	95.5	p=0.82
Yes	4.7	4.5	
Preterm birth (<37 weeks)			
No	94.9	94.2	p=0.55
Yes	5.1	5.8	

Distance to city park (m)			
≤ 300	26.6	25.0	p=0.74
300-999	60.2	61.4	
≥1000	13.2	13.6	

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[Within title page 1 and page 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 3-4]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 2 and 4]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Methods pages 4-5]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[pages 4-5]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **[page 5]**
		(*b*) For matched studies, give matching criteria and the number of controls per case **[NA]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 5-6]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 5-6]**
Bias	9	Describe any efforts to address potential sources of bias **[page 7]**
Study size	10	Explain how the study size was arrived at **[page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[pages 5-7]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[page 7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[page 7]**
		(*c*) Explain how missing data were addressed **[7, S1]**
		(*d*) If applicable, explain how matching of cases and controls was addressed **[NA]**
		(*e*) Describe any sensitivity analyses [**page 7]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[page 7-8, S1]**
		(b) Give reasons for non-participation at each stage **[NA]**
		(c) Consider use of a flow diagram [NA]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[pages 8-9, tables 1, 2]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure **[page 8, table 1, figures 1, 2]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[pages 10-13, tables 3, 4]**
		(*b*) Report category boundaries when continuous variables were categorized **[page 9]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[pages 10-13, Tables 3, 4]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[page 13-16]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[page 16-17]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[page 16-17]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[pages 17]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 18]**

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.