



Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Allergic symptoms in association with naturalness, greenness, and greyness: A cross-sectional study in schoolchildren in the Alps

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ARTICLE INFO

Keywords:

Allergic rhinitis
Asthma
Eczema
Greenness
Green space
Grey space
Greyness

ABSTRACT

Background: Greenness may protect from or contribute to allergy risk by influencing air pollution and human-microbe interactions. However, existing research on the issue is heterogeneous and produced conflicting results. Less is known about the effects of greyness. This study investigated the association between different characteristics of residential and school environment and allergic symptoms in schoolchildren.

Methods: The present cross-sectional survey was undertaken in 2004/2005 among 1251 schoolchildren (8–12 years old) in several alpine valleys in Austria and Italy. Children's mothers completed a questionnaire that asked about allergic symptoms (International Study of Asthma and Allergies in Childhood questionnaire), socio-demographic information, lifestyle, perinatal data, and housing conditions. We constructed four aggregate outcome variables: current asthma symptoms, ever asthma symptoms, ever allergic rhinitis (AR) symptoms, and ever eczema symptoms. We employed well-known greenness and greyness exposure indicators (Normalized Difference Vegetation Index, tree canopy cover, agricultural cover, imperviousness cover, and industrial cover), as well as an alternative naturalness index (Distance to Nature, D2N). Adjusted logistic regressions were used to explore associations between each exposure-outcome pair. Air pollution (NO₂), traffic noise and time spent outdoors were tested as potential mediators in causal mediation analysis.

Results: Decrease in naturalness in a 500-m buffer around the home was associated with higher prevalence of AR symptoms. Associations with asthma symptoms were in the same direction but marginally significant. Residential NDVI and tree cover were marginally associated with lower prevalence of asthma and AR symptoms. Having a domestic garden was associated with lower prevalence of asthma symptoms. School greenness in a 100-m buffer was associated with lower prevalence of AR symptoms. Residential greyness was associated with higher prevalence of AR and asthma symptoms. We observed stronger associations for greenness and greyness in non-movers and in children without a family history of allergies. Mediation by NO₂ and time spent outdoors was present in some of the exposure-outcome pairs.

Conclusions: Schoolchildren residing in places with lower naturalness and higher greyness may be more likely to have allergic rhinitis and possibly asthma. Considering more comprehensive indicators than greenness and greyness and conducting research in children without a family history of allergic diseases may be key to better understanding who can profit from natural landscapes.

1. Introduction

Asthma and allergic diseases are major contributors to the global

burden of childhood disease (Ferrante and La Grutta, 2018). They can also severely undermine children's health-related quality of life (Montalbano et al., 2020). Since 1960, asthma and allergy prevalence have

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<https://doi.org/10.1016/j.envres.2020.110456>

Received 21 September 2020; Received in revised form 2 November 2020; Accepted 7 November 2020

Available online 11 November 2020

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been soaring but increases are unevenly distributed (Platts-Mills, 2015). The International Study of Asthma and Allergies in Childhood (ISAAC) has shown differences by global region and country as well as across urban-rural and socioeconomic gradients (Asher et al., 2006; Rodriguez et al., 2019). Although the pathophysiology of asthma and allergic diseases is complex and a strong genetic component is evident (Ober and Yao, 2011), the substantial and rapid changes in its epidemiology over the past few decades point to complex gene-environment interactions (Murrison et al., 2019).

Allergy risk in childhood is shaped by myriad internal and external influences (Dick et al., 2014; Deng et al., 2016a, 2016b; Murrison et al., 2019). Notable risk factors include tobacco smoke (Ni et al., 2020), traffic-related air pollution (Deng et al., 2016a, 2016b; Khreis et al., 2017), mold and dampness (Tischer et al., 2011), prematurity (Sonnenchein-van der Voort et al., 2014; den Dekker et al., 2016; Zhang et al., 2018), viral infection (Feldman et al., 2015; Jackson et al., 2008) and antibiotic use (Patrick et al., 2020). Suggested protective factors encompass living on a farm (von Mutius and Vercelli, 2010; von Mutius, 2018), large family size (especially older siblings) (Karmaus and Botezan, 2002; Strachan et al., 2015), exclusive breastfeeding for at least 4 months (van Meel et al., 2017), and other dietary factors (McKeever and Britton, 2004). Existing evidence on the role of structured (e.g., parks) and unstructured (e.g., street trees) vegetation in the living environment remains controversial (Ferrante et al., 2020). For example, a protective role of vegetation ("greenness") has largely been attributed to air pollution mitigation (Janhäll, 2015). However, biodiverse vegetated areas can also support beneficial human-microbe interactions. Humans co-evolved with airborne and soil-based bacterial communities, which facilitate the maturation of the human immune system (Mhuiréach et al., 2016), which can prevent development of allergic diseases (Haahtela, 2019). Diverse vegetation around homes has been associated with health-related changes in skin (Hanski et al., 2012) and gut microbiota composition (Parajuli et al., 2020). Against this backdrop, exposure to farm animals (e.g., cows) and their production inputs and consumables (e.g., straw and "raw" unpasteurized milk) may protect against allergy in children (Riedler et al., 2000; Illi et al., 2012; Horak et al., 2014; Deckers et al., 2019). Domestic gardens can also provide rich outdoor microbiota exposure (Parajuli et al., 2020). In contrast, increased exposure to "greyness" (i.e., industrial, transport and urban-fabric landscapes) may reduce skin and intestinal commensal microorganism diversity and contribute to atopic disease risk (Logan, 2015; Haahtela et al., 2015; Segata, 2015).

Despite some promising findings for greenness and allergies, the cumulative analysis of extant research produces conflicting results (Ferrante et al., 2020). Heterogeneity in how and where greenness is estimated as well as unmodelled mediators and confounders may explain mixed results. Multicenter studies demonstrate variation in the effect of greenness across land uses and geographic contexts (Fuertes et al., 2014a, b, 2016; Tischer et al., 2017). Differences in species composition, microclimate conditions and pollution levels can display protective effects in rural areas and the opposite in urbanized areas (Fuertes et al., 2014a, b). Favored vegetation measures (e.g., Normalized Difference Vegetation Index; NDVI) have been shown to be insufficiently specific to detect health effects in some geographic contexts (Gernes et al., 2019). An example of this is one study in which exposure to higher green space coverage, coniferous forests in particular, was associated with increased respiratory disease in children, while an inverse relationship was suggested for agricultural space (Parmes et al., 2020). Focusing exclusively on greenness around the home may exclude important exposures in other activity spaces (cf. Kwan, 2012; Tischer et al., 2018). Potential mediating variables - e.g., air pollution (Zeng et al., 2020), time spent outdoors (cf. Logan, 2015) and traffic noise reduction (Van Renterghem et al., 2015) - have been modelled instead as confounders or altogether ignored, despite their potential to reduce the risk of respiratory diseases (Niemann et al., 2006; Ising et al., 2004; Khreis et al., 2017). Further, we are aware of only a handful of studies

that have simultaneously investigated the effects of greenness and greyness as a confounder on allergic diseases (Tischer et al., 2017, 2018; Cilluffo et al., 2018; Parmes et al., 2020).

The present study sets out to address these measurement and modelling gaps in the previous literature on the association between land use characteristics and allergies. We investigate this relationship in the context of several Alpine valleys with a predominantly rural to suburban landscape at altitudes between 600 and 1200-m. This unique setting is characterized by high vegetation biomass, biodiversity, and scenic beauty that coexists with high levels of traffic emissions in some of the valleys (Dzhambov et al., 2019). To overcome the aforementioned gaps in the literature, we examine numerous well-known greenness and greyness exposure indicators (e.g., NDVI, tree canopy cover, agricultural cover, imperviousness cover, and industrial cover) as well as an emerging comprehensive landscape index called "distance to nature" (D2N; Rüdiger et al., 2012). We explore potential mediation pathways through air pollution, traffic noise, and time spent outdoors as well as numerous modifiers thought to explain the observed effects on allergic symptoms.

2. Methods

2.1. Study area

The present study takes advantage of data collected within the BBT (Brenner Base Tunnel) survey in the Tyrol Region – the Lower Inn valley (Untertal) in Austria and the Wipp valley (Wipptal) and its side valleys on both sides of the Brenner Pass in Austria and Italy (Fig. 1). These valleys are part of the most important access route for heavy goods traffic over the Brenner Pass, which links central and northern Europe's traffic to southern Europe. The settlements consist of densely populated small towns and villages with a mix of industrial, small business, touristic, and agricultural activities (Dzhambov et al., 2019). Main transportation lines (a highway and a railway) run through the valleys and main roads connecting to the various small villages, which cause high levels of traffic noise (Lercher et al., 2008; Lercher and Botteldooren, 2006; von Lindern et al., 2016).

The narrow V-shaped Wipp valley extends along the river Sill southward from Innsbruck up to the Brenner Pass at the Austro-Italian border. South of the border, the valley stretches along the river Isarco down to Fortezza in Italy. The Lower Inn valley extends east of Innsbruck towards the Austrian-German border across a relatively broad U-shaped valley floor and up to the foothills of the Alpine comb. The area is characterized by a combination of high levels of air pollution and traffic noise (Lercher et al., 1995; Lercher and Kofler, 1996; Heimann et al., 2007). Owing to differences in meteorology and topography, air pollution levels in the Wipp valley are considerably lower than in the Lower Inn valley (Heimann et al., 2007).

2.2. Study design

The cross-sectional BBT survey was undertaken in 2004/2005 among 1251 children (response rate = 85.5%) recruited from 49 schools (grades 3–4; 8–12 years old) in the Wipp valley and the Lower Inn valley (Lercher et al., 2013). Children's mothers completed a self-administered, standardized questionnaire that asked about allergic symptoms, sociodemographic information, lifestyle, perinatal data, and housing conditions. Legal guardians of all participants provided written informed consent. Ethical approval for the original project proposal for which the data were collected was obtained in 2004 from the Ethics committee of the Medical University Innsbruck.

2.3. Allergic symptoms

To collect information on the presence of allergic symptoms in the child, the mother answered questions adapted from the ISAAC module

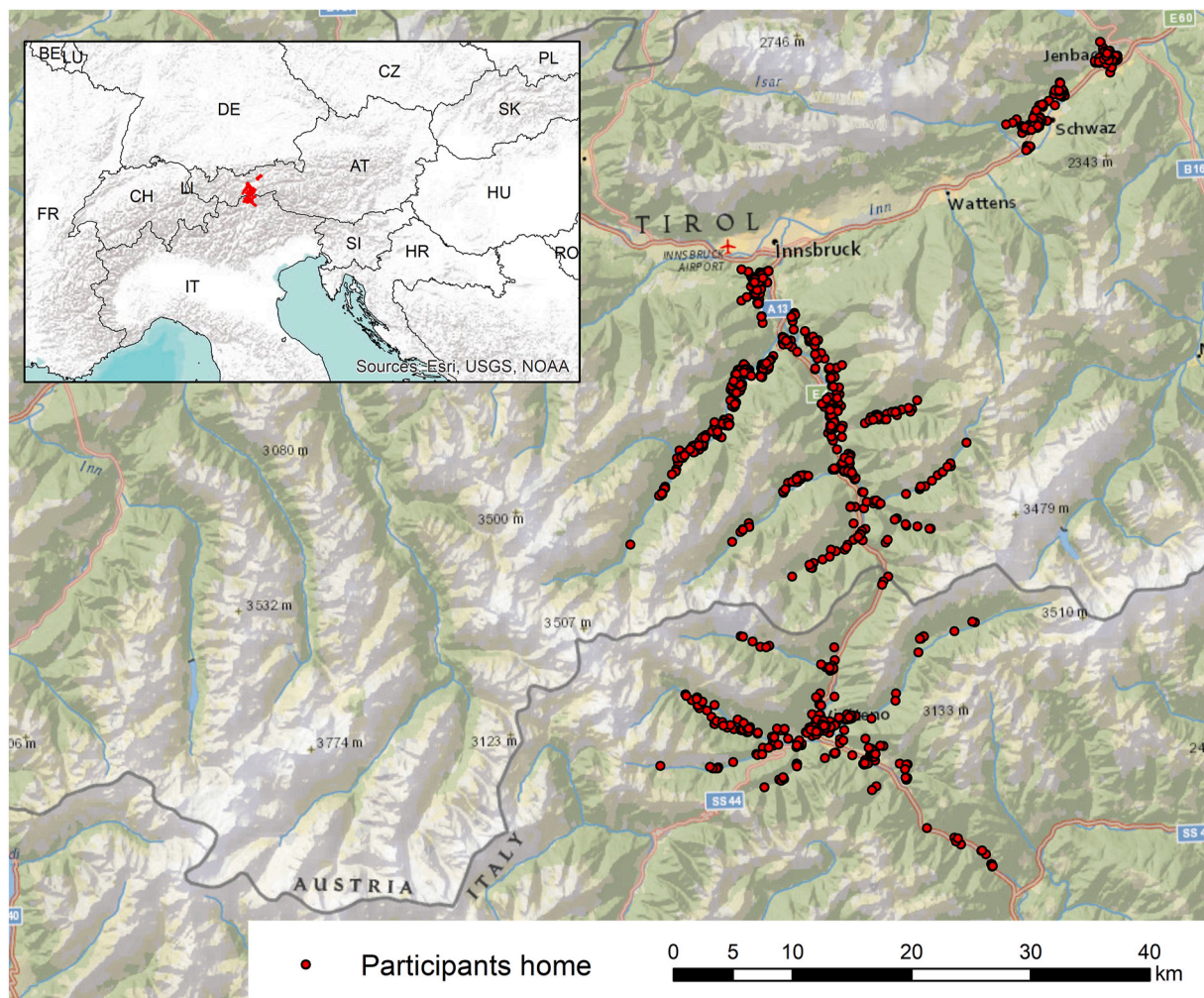


Fig. 1. Participants' home addresses in the BBT survey areas.

for 6–7 years olds (Asher, 1995, 1998) and questions on health status and medication intake. Based on their responses, we constructed four aggregate outcome variables for the present study. The combination of different ISAAC questions and symptoms found in the respective condition is an effective strategy to identify the prevalence of that condition (cf. Lukrafka et al., 2010; Magzoub et al., 2017). Aggregate outcome variables included:

- Current asthma symptoms were indicated by a positive response to any of the following: “In the last 12 months, has your child’s chest sounded wheezy during or after exercise?”; “In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?”; and/or “In the last 12 months, has your child taken medication against asthma?”.
- Ever asthma symptoms were confirmed by a positive response to either: “Has your child ever had asthma?” and/or “Has your child ever had wheezing or whistling in the chest at any time in the past?”.
- Ever allergic rhinitis (AR) symptoms were confirmed by an affirmative response to either: “Has your child ever had hay fever?” and/or “Has your child ever had a problem with sneezing or a runny or blocked nose, when he/she DID NOT have a cold or the ‘flu?’”.
- Ever eczema symptoms were confirmed by either: “Has your child ever had eczema?” and/or “Has your child ever had an itchy rash which was coming and going for at least six months?”.

2.4. Landscape indicators

Following previous studies (Ferrante et al., 2020), we include NDVI as a total greenness measure (Tucker, 1979) but also calculate other landscape indicators potentially associated with allergies. These include tree canopy cover; agricultural cover, which may be differentially associated with allergic symptoms (Parmes et al., 2020); greyness, as measured by imperviousness cover and industrial cover; and “distance to nature” (D2N; Rüdiger et al., 2012). All landscape indicators were estimated within Euclidean buffers with radii of 100, 500, and 1000-m surrounding the child’s home and with a radius of 100-m surrounding their school. The school buffer size was limited, because children have limited mobility while at school. Spatial analysis and GIS related tasks we conducted in ArcMap 10.6 or QGIS v3.8.

NDVI estimates the density of green (chlorophyll containing) vegetation using the difference in the intensities of reflected light in the red and near-infrared range divided by the sum of these intensities (Rhew et al., 2011). Healthy, green vegetation reflects more near-infrared and green light compared to other wavelengths and absorbs more red and blue light. NDVI ranges from -1 to $+1$, where positive values closer to 1 indicate high greenness (Gascon et al., 2016). In the current study, NDVI was calculated at a 30 m^2 resolution using satellite data from the Landsat 4–5 Thematic Mapper via the Semi-Automatic Classification Plugin (SCP) (Congedo, 2016) for QGIS (v3.8, <http://qgis.osgeo.org>). Cloud-free images from summertime (July–August in 2003) were selected to capture maximum spatial contrasts in greenness and because other seasons in the mountainous study region are partially covered with

snow. Following previous research (Dzhambov et al., 2019), we set all pixels with open/surface water as indicated on the Open Street Maps (<https://www.openstreetmap.org/>) to missing values to prevent suppressing the effect of greenness (Rugel et al., 2017).

Tree canopy cover was the percentage of surface covered by woody vegetation higher than 5 m. Cover estimates from the year 2000 were calculated at a 30 m² resolution using data from the University of Maryland Land-Cover/Land-Use Change Program (<https://lcluc.umd.edu/metadata/global-30m-landsat-tree-canopy-version-4>), which utilized all seven bands of the Landsat-5 Thematic Mapper (Sexton et al., 2013). These estimates have been employed and validated in prior research (Alexander et al., 2014).

Agricultural cover was evaluated at a minimum Mappable Unit (MMU) of 25 ha using the Corine Land Cover (CLC) inventory from the year 2000 (<https://land.copernicus.eu/pan-european/corine-land-cover/clc-2000/view>). Agricultural intensity was expressed as the proportion cover of pixels within each buffer size (Gardi et al., 2010). This measure ranged from 0.00 (no agricultural cover) to 1.00 (highest agricultural cover).

Imperviousness density was estimated as percentage of sealed soil area ranging from 0 to 100% based on the satellite data with a pixel resolution of 20 m². The so called ‘High Resolution Layer: Imperviousness Degree (IMD) 2009’ was processed and provided by the European Environment Agency (<https://land.copernicus.eu/user-corner/technical-library/hrl-imperviousness-technical-document-prod-2015>).

Industrial cover was estimated as the percentage of industrial and commercial area (CLC 1.2.1) using the CLC data from 2000. This variable ranged from 0.00 (no industrial cover) to 1.00 (complete industrial cover).

D2N quantifies the anthropogenic influence on a landscape by considering both the degree of habitat change caused by anthropogenic land use and the spatial distance to the nearest natural habitat (Rüdiger et al., 2012). D2N is calculated by multiplying two indicators: degree of naturalness and distance to natural habitat. These are normalized to range from 0 (natural/no distance) to 1 (artificial/far from natural habitat). The degree of naturalness indicator portrays biodiversity-relevant anthropogenic interferences on plants, animals, and ecosystems and hence classifies land cover categories along a seven-staged naturalness scale (e.g., natural, near-natural, semi-natural, altered, cultural, artificial with natural elements, and artificial). The distance to natural habitat indicator calculates the span to the nearest natural or near-natural patch. Indicator estimations were based on a set of different land use and land cover information (CORINE land cover, detailed agricultural land use data, detailed forest map, data on soil sealing, and transport infrastructure) merged to a new raster with a cell size of 25 m², as described by Rüdiger and colleagues (Rüdiger et al., 2012).

In addition to these remotely-sensed indicators, data on the presence of a domestic garden was collected in the questionnaire.

2.5. Covariates

Literature precedent and consistent evidence of biological, lifestyle and contextual factors guided our selection of covariates and modifiers (Dick et al., 2014; Murrison et al., 2019; Gernes et al., 2019; Tischer et al., 2017, 2018; Zeng et al., 2020). Sociodemographic data included child’s age and sex and maternal education (categorized as basic (9 years of school), skilled labor, vocational, or A-level). In Austria, maternal education is considered a good proxy for socioeconomic position, which we have used successfully in an earlier child study in this area (Lercher and Schmitzberger, 1997). The early biological exposome included low birth weight (<2500 vs ≥ 2500 g), smoking during pregnancy (no vs. yes), and duration of breastfeeding (in months). These perinatal data were extracted from the “Mother and Child Passport” (for Austrian children) or “Mother Passport” (for Italian children), which every pregnant women in the study area completes in accordance with

physician medical records (Bancher-Todesca, 2014). Owing to the low number of cases in secondhand smoke exposure and diagnosed pneumonia or bronchitis during the first year of life, we combined these measures into an ordered, integer-level cumulative risk index (0–3). This risk index is justified from a theoretical stance because all three factors contribute to adverse airway remodeling (Savenije et al., 2012; Feldman et al., 2015). Mother-reported parental family history of allergy (asthma, allergic rhinitis (AR), or eczema) was collected as a binary variable (no vs yes). We also calculated the number of green months (April to September) during the pregnancy, as season of birth may be a predictor of atopic manifestations (e.g., due to tree pollen exposure) (Nilsson et al., 1997; Kuwabara et al., 2020).

Mothers also provided information on their child’s living conditions. This information included crowding in the household (people-to-rooms ratio), mold/dampness ever in the home (no vs. yes), presence of a pet in the home during the first year of the child’s life (no vs. yes), living on a farm (no vs. yes), and duration of residence at the current address.

We also accounted for the geographic region (valley) where the child lived. These included five locales: Inn valley, Wipp valley north (side), Wipp valley south (side), Wipp valley north (main), and Wipp valley south (main). Each region displays slight differences in topography and traffic emissions (Dzhambov et al., 2019).

2.6. Putative mediators

Based on our literature review and available data, we examined three potential mediators of the association between landscape characteristics and allergic symptoms: air pollution, traffic noise and time spent outdoors.

Annual means for NO₂ in 2003/2004 were calculated for seven overlapping model domains along the Wipp valley (>300 km²) and for an area 27 km (W-E) × 23 km (N-S) east of Innsbruck in the Inn valley (Dzhambov et al., 2019). For these air quality assessments, approximately 300 flow fields were calculated with the meteorological model GRAMM (Graz Mesoscale Model) for each domain and sub-domain (up to 100 m² resolution). Traffic emissions modeling relied on the network emission model NEMO and real time measurements on the road to account for higher emissions under load (slope between 3 and 5%). For each flow field, a dispersion simulation with the Lagrangian particle model GRAL was calculated for horizontal resolutions of 10 m² with a vertical resolution of 2 m. Annual, summer, and winter means were calculated by weighting the numerous dispersion calculations. The modeling resolved the dispersion processes close to strong sources such as busy roads. Model results were evaluated against measurements from existing air quality monitoring stations located very close to strong emission sources and field measurements in inhabited areas. A full outline of the modelling is provided by Öttl et al. (2007).

An early version of the Harmonoise source model was used to calculate road noise emissions in 2003/2004 (Jonasson, 2007). Calculations were supplemented with additional traffic counting and micro-simulations of the traffic flow (Paramics). Railway noise emissions were measured during a typical day with several long-term sound recorders located 25 m from the railway tracks. Sound modelling was carried out with Bass3, an extended version of ISO 9613. The validity of these simulations was calibrated against measurement results from extensive sound monitoring campaigns during the previous summer and winter. Because railways are absent in side valleys, road and railway traffic were not considered as separate noise sources. Total day-evening-night noise level (L_{den}) was calculated at the most exposed façade, reflecting only road traffic noise for residents of the side-valleys and combined road traffic and railway noise for those living in the Wipp valley (Dzhambov et al., 2019).

In the questionnaires, mothers provided information on the average time her child spent outdoors in the summer per day. This categorical variable was right skewed, so we dichotomized it for the analyses (≤6 vs. > 6 h/d).

2.7. Statistical analysis

Inspection of the dataset revealed that few children had missing data in the variables of interest; therefore, we conducted complete-case analyses without imputing missing values and the analytic sample varies across analyses. The variables with the largest proportion of missing values were ever eczema ($n = 66$, 5.3%), family history of allergic diseases ($n = 82$, 6.6%), and NO_2 ($n = 114$, 9.1%). We calculated descriptive statistics to inspect the distribution of all exposure and outcome variables. To investigate general patterns of association in the data, we used t-tests, ANOVAs, Fisher/Fisher-Freeman-Halton exact tests, Mood's median tests, and Pearson correlation coefficients.

Logistic regressions were fitted to assess prevalence of current asthma, ever allergic rhinitis (AR), ever eczema and ever asthma symptoms in relation to each environmental indicator and potential mediator. Given the possibility for under or overadjustment and inconsistent treatment of confounding, we report several models with increasing adjustment. Initial models were adjusted for child's age and gender, maternal education and region. These were followed by main models additionally adjusting for low birth weight, smoking during pregnancy, breastfeeding, cumulative risk of smoking, pneumonia or bronchitis in the first year, and green months during pregnancy. Fully adjusted models further controlled for living on a farm, crowding in the household, presence of mold/dampness in the home, and pet in the home in the first year. These models did not suffer from multicollinearity according to tolerance (>0.2) and Variance Inflation Factor (<5.0) values. In a previous study based on the same data (Dzhambov et al., 2019), we found that the major spatial differences and clusters were observed on valley-level rather than on community-level. Given the potential for biased estimates of the standard errors as a result of the small number of such clusters (cf. Maas and Hox, 2005), we decided to employ a fixed effects approach to clustering by adjusting for geographic region, in lieu of multilevel modeling.

Causal mediation analysis was conducted to test whether NO_2 , L_{den} and time spent outdoors mediated associations in models with 500-m buffers. This counterfactual modeling approach (Robins and Greenland, 2000) is increasingly used in environmental epidemiology (Dzhambov et al., 2020). We used the "paramed" module for Stata (Emsley and Liu, 2013) to estimate the total, controlled direct, and natural indirect effects of landscape characteristics on allergic symptoms. Standard errors and confidence intervals were derived using bootstrapping (1000 samples). Mediation was indicated when the indirect path significantly exceeded zero, regardless of the significance of the total effect (Zhao et al., 2010).

Next, we conducted stratified analysis and tested potential effect modification by gender, maternal education, crowding, breastfeeding, pet, mold/dampness, living on a farm, time spent outdoors, region, and NO_2 . We present effect estimates across levels (subgroups) of all pre-specified putative modifiers, regardless of the presence of a significant interaction term. These analyses were limited to the $D2N$ indicator for the 500-m radius because it was the most comprehensive and consistently performing indicator in our study (see Results). For these tests, breastfeeding (<4 vs ≥ 4 months), crowding (<1 vs ≥ 1) and NO_2 (<12.68 vs $\geq 12.68 \mu\text{g}/\text{m}^3$) were split at the median. The criterion for statistical consideration of interactions was relaxed to $p < 0.1$ (i.e., Type I error rate of 10%) (Selvin, 1996; Greenland and Rothman, 1998; Marshall, 2007).

In subgroup analysis, we limited the main logistic regressions to children who had lived in the same home since birth to reduce exposure misclassification (Norbäck et al., 2018). We also repeated the analysis in children without a family history of allergic diseases.

Data were processed with SPSS v. 23 and Stata v. 14. Associations were considered statistically significant at the $p < 0.05$ level (two-tailed), except for interactions in the effect modification models.

3. Results

3.1. Characteristics of the study population and bivariate associations

Characteristics of the children are presented in Table 1 and bivariate associations with child's allergic symptoms' status are presented in Supplementary Tables S1 and S2. Higher cumulative risk in the first year

Table 1
Study population characteristics.

Characteristics	N (%) / Mean $\pm$ SD / Median $\pm$ IQR
Socio-demographics	
Age [years] (Mean $\pm$ SD)	9.36 $\pm$ 0.65
Male (N, %)	623 (49.8)
Maternal education (N, %)	
Basic	279 (22.3)
Skilled labor	396 (31.7)
Vocational	287 (22.9)
A-level	247 (19.7)
Allergic symptoms (N, %)^a	
Current asthma	250 (20.0)
Ever allergic rhinitis	311 (24.9)
Ever eczema	258 (20.6)
Ever asthma	265 (21.2)
Early biological exposome	
Low birth weight (N, %)	77 (6.2)
Pregnancy smoking (N, %)	146 (11.7)
Cumulative risk 1st year (N, %) ^b	
0 factors	849 (67.9)
1 factor	320 (25.6)
2 factors	36 (2.9)
3 factors	5 (0.4)
Breast feeding [months] (Median $\pm$ IQR)	4.00 $\pm$ 7.00
Family history of allergies (N, %)	421 (33.7)
Green months during pregnancy (Median $\pm$ IQR)	5.00 $\pm$ 3.00
Living conditions	
Crowding [people/rooms] (Mean, IQR)	1.09 $\pm$ 0.41
Pet in the home during 1st year (N, %)	221 (17.7)
Mold/dampness (N, %)	314 (25.1)
Living on a farm (N, %)	168 (13.4)
Presence of domestic garden (N, %)	1175 (93.9)
Distance to nature	
$D2N_{500\text{-m}}$ (Median $\pm$ IQR)	0.21 $\pm$ 0.13
Residential greenness	
$\text{NDVI}_{500\text{-m}}$ (Mean $\pm$ SD)	0.50 $\pm$ 0.07
Tree cover 500-m [%] (Mean $\pm$ SD)	34.68 $\pm$ 9.32
Agricultural cover 500-m (Median $\pm$ IQR)	0.36 $\pm$ 0.28
Residential greyness	
Imperviousness 500-m [%] (Median $\pm$ IQR)	12.74 $\pm$ 20.40
Industrial cover 500-m (Median $\pm$ IQR)	0.40 $\pm$ 0.41
Putative mediators	
L_{den} [dBA(A)] (Mean $\pm$ SD)	52.51 $\pm$ 11.32
NO_2 [$\mu\text{g}/\text{m}^3$] (Mean $\pm$ SD)	15.97 $\pm$ 9.34
Time spent outdoors [> 6 h/d] (N, %)	530 (42.4)
School exposure	
$D2N_{100\text{-m}}$ (Mean $\pm$ SD)	0.40 $\pm$ 0.14
$\text{NDVI}_{100\text{-m}}$ (Mean $\pm$ SD)	0.34 $\pm$ 0.11
Tree cover 100-m [%] (Median $\pm$ IQR)	26.66 $\pm$ 10.91
Agricultural cover 100-m (Median $\pm$ IQR)	0.00 $\pm$ 0.14
Region (N, %)	
Inn valley	251 (20.1)
Wipp valley north (side)	326 (26.1)
Wipp valley south (side)	133 (10.6)
Wipp valley north (main)	326 (26.1)
Wipp valley south (main)	215 (17.2)

Abbreviations: $D2N$ – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

^a Current asthma = wheezing, dry cough at night and/or medication against asthma in the last 12 months; Ever allergic rhinitis = hay fever or non-cold-related sneezing, runny or blocked nose at any time in the past; Ever eczema = eczema or an itchy rash for at least six months; Ever asthma = asthma or wheezing/whistling at any time in the past.

^b Cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life.

of life and presence of mold/dampness in the home were associated with higher prevalence of current and ever asthma symptoms. Family history of allergies was predictive of all allergic outcomes in children. Conversely, living on a farm was related to lower likelihood of current asthma symptoms and ever AR symptoms. Higher NDVI, lower *D2N* (more natural landscape elements), and less industrial cover in the 500-m buffer was associated with lower ever prevalence of AR symptoms. Having a domestic garden was associated with lower current prevalence of asthma symptoms. Higher NO₂ exposure contributed to asthma symptoms. Children with ever eczema symptoms had higher tree cover in their residential environment.

Supplementary Table S3 shows intercorrelations between the exposure and mediator variables. *D2N* was inversely related to NDVI, tree cover, and agricultural cover and positively to imperviousness and industrial cover. Residential greenness was negatively correlated with greyness and positively with school greenness. Living in a greener environment was associated with lower *L_{den}* and NO₂ exposure and more time spent outdoors.

3.2. Associations between landscape characteristics, mediators and allergic symptoms

Higher *D2N* was associated with higher prevalence of ever AR symptoms, and associations with current and ever asthma symptoms went in the same direction but were marginally significant (Table 2). In the fully adjusted models (Supplementary Table S5), the effect of *D2N* on AR persisted in the 500-m (1.23; 95% CI: 1.01, 1.50) and 1000-m buffers (1.28; 95% CI: 1.00, 1.63), although it was reduced by 10%.

NDVI and tree cover were marginally associated with lower prevalence of asthma and AR symptoms (Table 2 and Table S4). School greenness (NDVI and tree cover) was associated with lower prevalence of ever AR symptoms, although the other estimates were small and non-significant. Results for agricultural cover were unclear. Having a domestic garden was associated with lower asthma symptoms prevalence. In the minimally adjusted models, some effects (for NDVI and domestic garden) turned significant and in general increased in magnitude (Supplementary Table S5). For eczema symptoms, associations were

weak and inconsistent depending on the greenness indicator.

Imperviousness and industrial cover were strongly associated with higher prevalence of ever AR symptoms. In addition, greyness, especially higher imperviousness, was associated with asthma symptoms.

Regarding putative mediators, NO₂ was strongly related to current asthma symptoms. Spending more time outdoors was associated with lower prevalence of current asthma symptoms and ever AR symptoms. *L_{den}* was only marginally associated with current asthma symptoms. In the fully adjusted models (Supplementary Table S6), the effects of imperviousness_{100-m} and NO₂ were not diminished.

3.3. Mediation of the association between residential landscape characteristics and allergic symptoms

We found only one mediator of the effect of *D2N*. An increase in *D2N* led to higher NO₂ levels and, in turn, higher prevalence of current asthma symptoms (Table 3). Greater NDVI and tree cover were related to lower NO₂ levels, and, in turn, lower odds of current asthma symptoms. In contrast, imperviousness and industrial cover contributed to current asthma by increased NO₂ levels. Another pathway from imperviousness to asthma and AR symptoms went through less time spent outdoors. Supplementary Tables S7–S10 show mediation tests for all landscape characteristics and outcome measures.

3.4. Effect modification of the associations between distance to nature and allergic symptoms

Stratified results for *D2N* are presented in Supplementary Table S11. Overall, effect modification was present in few cases. *D2N* was more strongly associated with ever asthma symptoms in children living on a farm (OR = 1.67; 95% CI: 0.79, 3.55) compared with their counterparts (OR = 1.09; 95% CI: 0.88, 1.36). In addition, *D2N* was stronger associated with ever asthma when crowding at the home was higher (OR = 1.20; 95% CI: 0.93, 1.54) than when it was lower (OR = 1.13; 95% CI: 0.76, 1.69). For ever eczema symptoms, higher *D2N* related to lower prevalence in boys (OR = 0.62; 95% CI: 0.45, 0.85) but not in girls (OR = 1.25; 95% CI: 0.93, 1.70). Compared to children of mothers with basic

Table 2
Associations between landscape characteristics and allergic symptoms.

	Current asthma		Ever allergic rhinitis		Ever eczema		Ever asthma	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Exposure indicator (analytic sample)								
<i>D2N</i> _{500-m}	1112	1.21 (0.98, 1.48)	1110	1.32 (1.09, 1.60)^a	1082	0.91 (0.74, 1.13)	1104	1.13 (0.92, 1.38)
Residential greenness	1112		1110		1082		1104	
NDVI _{500-m}		0.80 (0.63, 1.02)		0.83 (0.67, 1.03)		0.95 (0.75, 1.21)		0.81 (0.64, 1.03)
Tree cover _{500-m}		0.86 (0.66, 1.12)		0.86 (0.68, 1.09)		1.22 (0.95, 1.56)		0.94 (0.73, 1.22)
Agricultural cover _{500-m}		1.01 (0.81, 1.28)		0.88 (0.71, 1.08)		0.96 (0.77, 1.20)		0.92 (0.73, 1.15)
Domestic garden _{500-m}	1107	0.72 (0.51, 1.01)	1105	0.85 (0.62, 1.17)	1077	1.08 (0.76, 1.52)	1099	0.71 (0.51, 1.00)
Residential greyness	1112		1110		1082		1104	
Imperviousness _{500-m}		1.30 (0.99, 1.71)		1.35 (1.05, 1.73)^a		0.93 (0.71, 1.23)		1.24 (0.95, 1.63)
Industrial cover _{500-m}		1.25 (0.95, 1.64)		1.33 (1.04, 1.71)^a		0.88 (0.67, 1.15)		1.24 (0.94, 1.62)
Putative mediators								
<i>L_{den}</i>	1087	1.10 (0.95, 1.29)	1086	1.02 (0.89, 1.18)	1058	0.93 (0.80, 1.08)	1081	0.92 (0.79, 1.08)
NO ₂	1020	1.57 (1.22, 2.03)^a	1016	1.02 (0.79, 1.32)	991	1.02 (0.78, 1.33)	1009	1.23 (0.94, 1.61)
Time outdoors	1083	0.70 (0.51, 0.97)^a	1082	0.72 (0.54, 0.97)^a	1056	0.93 (0.68, 1.27)	1078	0.86 (0.63, 1.17)
School exposure	1111		1109		1081		1104	
<i>D2N</i> _{100-m}		1.01 (0.78, 1.31)		1.16 (0.92, 1.48)		1.02 (0.79, 1.32)		0.98 (0.76, 1.27)
NDVI _{100-m}		0.96 (0.82, 1.12)		0.86 (0.74, 0.99)^a		0.96 (0.83, 1.12)		0.99 (0.85, 1.15)
Tree cover _{100-m}		0.89 (0.69, 1.15)		0.73 (0.57, 0.94)^a		0.92 (0.72, 1.17)		0.93 (0.73, 1.19)
Agricultural cover _{100-m}		0.96 (0.87, 1.06)		0.93 (0.85, 1.02)		0.96 (0.88, 1.05)		1.01 (0.92, 1.10)

Abbreviations: *D2N* – Distance to nature, *L_{den}* – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide. Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover), per 10 dB(A) (*L_{den}*), per 10 µg/m³ (NO₂), for presence vs. absence of a domestic garden and for spending >6 h/day outdoors.

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region.

^a Estimate is statistically significant at the $p < 0.05$ level.

Table 3

Mediation of the association between residential distance to nature and allergic symptoms.

Effect of $D2N_{500-m}$	Current asthma symptoms	Ever allergic rhinitis symptoms	Ever eczema symptoms	Ever asthma symptoms
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NO₂ pathway				
Conditional direct effect	1.10 (0.86, 1.40)	1.33 (1.06, 1.61) ^a	0.95 (0.75, 1.20)	1.14 (0.90, 1.42)
Natural indirect effect	1.08 (1.03, 1.15) ^a	0.99 (0.94, 1.03)	1.01 (0.96, 1.06)	1.04 (0.99, 1.10)
Total effect	1.19 (0.94, 1.50)	1.31 (1.05, 1.60) ^a	0.96 (0.77, 1.20)	1.18 (0.93, 1.47)
L_{den} pathway				
Conditional direct effect	1.12 (0.93, 1.40)	1.35 (1.09, 1.63) ^a	0.92 (0.74, 1.18)	1.10 (0.89, 1.31)
Natural indirect effect	1.00 (1.00, 1.02)	1.00 (0.99, 1.01)	1.00 (0.98, 1.00)	1.00 (0.98, 1.00)
Total effect	1.13 (0.93, 1.39)	1.35 (1.09, 1.64) ^a	0.92 (0.74, 1.18)	1.10 (0.89, 1.31)
Time outdoors pathway				
Conditional direct effect	1.12 (0.93, 1.39)	1.24 (1.00, 1.51)	0.89 (0.69, 1.11)	1.06 (0.87, 1.30)
Natural indirect effect	1.01 (1.00, 1.05)	1.01 (1.00, 1.04)	1.00 (1.00, 1.03)	1.01 (0.99, 1.03)
Total effect	1.14 (0.94, 1.42)	1.26 (1.02, 1.54) ^a	0.89 (0.71, 1.13)	1.07 (0.88, 1.31)

Abbreviations: $D2N$ – Distance to nature, L_{den} – total day-evening-night noise level; NO₂ – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase in distance to nature. Confidence intervals for these estimates were derived using bootstrapping (1000 samples).

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region.

^a Estimate is statistically significant at the $p < 0.05$ level.

education, $D2N$ was negatively associated with ever eczema in children with mothers with skilled laborer educational levels (OR = 0.57; 95% CI: 0.36, 0.90). Higher $D2N$ was associated with lower prevalence of eczema only in children who had been breastfed for less than 4 months (OR = 0.78; 95% CI: 0.57, 1.08 vs. OR = 1.02; 95% CI: 0.76, 1.37).

3.5. Sensitivity analyses

Results of the sensitivity analyses are shown in [Supplementary Table S12](#). When analyses were restricted to children who had lived at the same address since birth, associations with greenness and greyness became stronger. Domestic garden was clearly related to lower current (OR = 0.59; 95% CI: 0.38, 0.91) and ever (OR = 0.63; 95% CI: 0.40, 0.97) prevalence of asthma symptoms in this subgroup, unlike in the full sample. In a 500-m buffer, tree cover was associated with more eczema symptoms (OR = 1.69; 95% CI: 1.21, 2.35), and imperviousness (OR = 0.67; 95% CI: 0.47, 0.97) and industrial cover (OR = 0.65; 95% CI: 0.46, 0.93) were associated with lower prevalence of eczema. The effect of $D2N$ was reduced and turned marginally significant. The significant effect of NO₂ on current asthma symptoms persisted.

For children without a family history of allergies, NDVI was related to lower odds of current (OR = 0.60; 95% CI: 0.43, 0.84) and ever asthma (OR = 0.65; 95% CI: 0.47, 0.91). Likewise, $D2N$ was associated with more current and ever asthma symptoms (OR = 1.33; 95% CI: 1.00, 1.77 and OR = 1.35; 95% CI: 1.02, 1.79). Greater imperviousness and industrial cover related to 79% and 78% higher odds of current asthma and 63% and 56% higher odds of ever asthma. Again, the effect of NO₂ remained robust.

4. Discussion

4.1. General findings

This study investigated the association between landscape characteristics and allergic symptoms of 8–12-years-old children residing in the Tyrol region (the Austrian/Italian Alps). Overall, residing in places with more anthropogenic influence on the landscape and less natural elements contributed to allergic rhinitis (AR) and asthma symptoms, whereas naturalness in the school surroundings did not appear important.

The composite landscape index $D2N$ performed better than other measures of greenness, like NDVI. The estimate for AR symptoms associated with $D2N$ persisted even in fully-adjusted models, though estimates for NDVI and tree cover did not. These findings can be attributed

to the fact that $D2N$ is a comprehensive measure that reflects the joint impact of greenness and greyness. To our knowledge, only [Tischer et al. \(2018\)](#) have attempted to overcome the limitations of commonly used unidimensional greenness indicators (e.g., NDVI). They constructed two environmental scores: an “outdoor-green score” from NDVI and CORINE and an “outdoor-grey score” from CORINE, NO₂, and road proximity. However, in that study, there were no associations between these comprehensive measures and respiratory or allergic conditions ([Tischer et al., 2018](#)).

Our findings for greenness, as measured by NDVI and tree cover, are in accordance with findings from previous studies. In many cases, greater overall greenness appears to be protective against asthma ([Lovasi et al., 2008](#); [Eldeirawi et al., 2019](#); [Sbihi et al., 2015](#); [Li et al., 2019](#); [Squillacioti et al., 2020](#)). Yet the literature is not at all consistent and several studies have failed to find any effect ([Tischer et al., 2018](#); [Gernes et al., 2019](#)) or have observed an increased risk of allergic respiratory diseases and allergic sensitization ([Dadvand et al., 2014](#); [Lovasi et al., 2013](#); [Andrusaityte et al., 2016](#)). What is more, the direction and strength of these associations varies by greenness indicator (e.g., NDVI vs. proximity) ([Dadvand et al., 2014](#)), population group ([Feng and Astell-Burt, 2017](#)), and geographic region ([Tischer et al., 2017](#)). For example, in one study ([Dadvand et al., 2014](#)), living closer to a green space was associated with higher prevalence of asthma, and greater surrounding greenness (NDVI) and proximity to forests were not. In another study, green space coverage interacted with exposure to road traffic in a way that children exposed to high traffic volumes had either elevated or reduced odds of asthma depending on the percentage of green coverage, without effects of green space in children not exposed to heavy traffic ([Feng and Astell-Burt, 2017](#)). A striking example of the heterogeneity in the body of evidence is a pooled analysis of seven birth cohorts, which evidenced differential associations between NDVI and AR, ranging from protective in some areas to harmful in others ([Fuertes et al., 2016](#)). One explanation could be that these effects depend on urbanization level ([Fuertes et al., 2014](#)). That our study area was predominantly rural and that rural lifestyle factors may be associated with protection against allergies ([Frei et al., 2019](#)) could explain why lower $D2N$ consistently contributed to AR. Other studies conducted in urban areas have failed to demonstrate such protective associations ([Dadvand et al., 2014](#); [Lovasi et al., 2013](#)). Another plausible explanation could be the high greenness level in our study area; however, this explanation does not seem exhaustive because some of the studies with low greenness level found a protective effect on asthma ([Li et al., 2019](#); [Squillacioti et al., 2020](#)). Another contributing factor may be that mountain soils contain highly diverse microbial communities ([Adamczyk et al.,](#)

2019; Praeg et al., 2019) and children living in these settings are exposed to farming life (e.g., even children who do not live on a farm may be engaged in helping at a local farm), which is a strong protective factor against allergy (Illii et al., 2012; Horak et al., 2014; Nielsen et al., 2020). However, unlike Parmes et al. (2020), we observed no protective effect of agricultural cover.

Our findings do not agree with earlier studies that found a weak or absent effect of greyness on allergic outcomes (Tischer et al., 2017; Ebisu et al., 2011; Parmes et al., 2020). Here, imperviousness and industrial cover were strongly associated with AR. A similar (marginally significant) trend was observed for asthma. This is in line with the “dysbiotic drift” hypothesis, which posits that reduced skin and intestinal commensal microorganism diversity may contribute to atopy (Logan, 2015). We believe that what allowed us to observe such consistent findings could be the abundant vegetation biomass and easy access to farm life strongly contrasting with the built environment features in children’s home surroundings, which created sufficient variability in exposure. We also used spatial data of high quality and spatial resolution.

None of the landscape characteristics were associated with eczema. This finding was unexpected, given that rural living and early-life exposure to biodiversity are expected to protect against eczema similarly to respiratory allergic outcomes (Bonamonte et al., 2019). Since most research to-date has focused on asthma and AR, we have limited basis for comparison. For example, one study on ever eczema found no effect of surrounding NDVI greenness and distance to a park (Li et al., 2019). According to another study, residential green space could buffer the effect of traffic-related air pollution on infant atopic dermatitis (Lee et al., 2018). We can offer no clear-cut explanation of this finding.

We are aware of only one earlier study on school greenness in relation to allergic outcomes. It found lower prevalence of asthma and wheezing in China was associated with increasing NDVI in a 1000-m buffer (Zeng et al., 2020). Although we did not find an effect on asthma, higher greenness surrounding schools in a 100-m buffer was associated with lower odds of AR. It was not feasible to test greenness in larger buffers like Zeng et al. (2020) because of the overlap between residential and school exposure in our study area. We believe residential greenness to be driving the effect in our study. Elementary school-children in this area spend a maximum of 5 h/day at school and distances from home to school are generally too small for a meaningful change in greenspace with a 500-m radius.

Although not consistent, living in a home with a garden showed a trend toward lower prevalence of asthma and AR. This is a novel finding and fits quite well into the broader literature. This semi-rural area is characterized by a large amount of single and double homes with gardens. Depending on the composition, gardens can provide a close biodiverse neighborhood and rich outdoor microbiota exposure (Parajuli et al., 2020), which seems protective against asthma development (Fyhrquist et al., 2014; von Mutius, 2016; Ruokolainen et al., 2017; Loverdos et al., 2019).

Overall, our findings may inform public health policy in rural areas. Conservation of natural land cover, and by extension protecting traditional lifestyle exposures, may confer health benefits on a population-level and thus complement targeted interventions for primary prevention of child allergy, such as exposure to bacterial lysates, bacterial and dietary metabolites, or helminthic compounds (von Mutius and Smits, 2020), which may not be widely available.

4.2. Mediating pathways

Previous studies on this topic have rarely conducted formal tests of potential pathways underlying the effect of greenness, and no study has tested pathways from both greenness and greyness. We found that higher naturalness and greenness, as measured by different indicators, were associated with lower prevalence of current asthma symptoms through lower NO₂ levels. Residential greyness, on the other hand, was

related to higher NO₂ and in turn to higher prevalence of asthma. The detrimental effect of NO₂ on current asthma was our most robust finding across all adjustment scenarios and sensitivity analyses. This is not surprising, given that air pollution is a well-known risk factor for childhood asthma (Bowatte et al., 2017; Khreis et al., 2017). On the one hand, plants release pollen, volatile organic compounds (VOCs) and other allergens (Antonelli et al., 2020), which can cause sensitization and atopic reactions (Cecchi et al., 2018). Air pollutants are known to modify viability, germination and chemical composition of pollen grains leading to the release of pollen penetrating more deeply in the respiratory tract (Sénéchal et al., 2015). On the other, certain type of vegetation can reduce harmful levels of air pollution by dispersion and deposition of particles on plant surfaces (Janhäll, 2015) and VOCs from anthropogenic sources (Yeager et al., 2020), but the actual reduction in particulate matter through parks or neighborhood greenness may be small (Xing and Brimblecombe, 2019). We are aware of only one other study that formally tested air pollution as a mediator of the effect of greenness on allergic diseases (Zeng et al., 2020). The authors found that reduced air pollution mediated the inverse associations between school greenness and asthma and wheezing in schoolchildren.

Despite the proposition that noise reduction is one of the pathways linking greenness to better health (Markevych et al., 2017) and tentative evidence that traffic noise might contribute to respiratory and allergic illness (Niemann et al., 2006; Ising et al., 2004; Tobías et al., 2014; Dzhambov and Dimitrova, 2017), we observed that the effect of L_{den} was weak and inconsistent. Noise-induced psychophysiological stress and sleep disturbance can alter the immune system through a cascade of neurochemical processes and thus contribute to bronchomotor tone dysregulation, airway inflammation, and increased susceptibility to respiratory infection (Recio et al., 2016). At the same time, green infrastructure in the form of tree belts and other green barriers can physically block and disrupt sound wave propagation (Van Renterghem et al., 2015) and alleviate the psychological stress induced by noise (Van Renterghem and Botteldooren, 2016; Van Renterghem, 2019). Our null finding may be attributable to the high correlations between air pollution and noise exposures. A recent study also failed to establish any evidence that traffic noise was associated with childhood asthma (Wallas et al., 2020).

Higher greyness was associated with less time spent outdoors and in turn with asthma and AR symptoms. Spending more time outdoors likely increased opportunities for contact with animal and plant biodiversity.

4.3. Supporting findings (effect modification and sensitivity analyses)

In terms of effect modifiers, the direction of the relationship between D2N and eczema varied by gender, with lower naturalness protective only in males. A similar trend was found by Li et al. (2019). We also found that lower naturalness was associated with lower prevalence of eczema only in children who had been breastfed for less than 4 months, but this association was not present with other allergy outcomes and requires further investigation. Basic maternal education was associated with stronger positive association between D2N and eczema and ever asthma. Living on a farm seemed to potentiate the association of greater D2N with ever asthma, which is in line with the hygiene hypothesis (von Mutius and Vercelli, 2010; Illii et al., 2012).

We observed stronger associations for greenness and greyness in non-movers, likely because environmental indicators more accurately reflected children’s long-term exposure with this subgroup. An unexpected pattern emerged in non-movers, however; higher naturalness and tree cover were associated with higher odds of eczema, and higher greyness was associated with lower odds of eczema. This is challenging to explain and future studies should investigate this outcome further.

Interestingly, in the subgroup without a family history of allergies, the effect of greenness (NDVI) and greyness on asthma increased considerably. We suspect that the strong heritability in the BBT sample partly obscured the contribution of environmental influences

(Ober and Yao, 2011), which became pronounced when the genetic component was eliminated. Failing to account for allergies history could be one explanation for the null findings in earlier research. Future studies should stratify by family history of allergic disease and probe for gene-environmental interactions.

4.4. Strengths and limitations

The present study has a number of strengths. The predominantly rural mountainous area, with high vegetation biomass, species richness, microbial biodiversity and farm life, provides a unique setting to examine mediation by high traffic-related pollution and noise loads during early-life. Also, unlike past research, we evaluated both residential and school greenness and greyness. Furthermore, this is also one of the few studies to look into eczema in relation to landscape characteristics. It is only the second study to test pathways to allergic symptoms through air pollution and the first to test pathways through traffic noise and time spent outdoors. Future studies are encouraged to explore such mechanisms, because focusing only on the total effect of landscape characteristics on health might generate misleading results (Dzhambov et al., 2020). Drawing on earlier literature, we considered a rich covariate set, including contextual, biological and lifestyle factors believed to impinge on allergic disorders. Our finding of effect modification by family history of allergies is also novel. Finally, we relied on state-of-the-art methods tailored specifically to this alpine region to model air pollution and noise.

Owing to the diversity of the surrounding natural habitat in the study area, we employed a new indicator of naturalness (*D2N*) that provides spatial explicit assessment of land use effects on the environment to capture both land use intensity and proximity to natural habitats. As such, *D2N* predicts both biodiversity (Rüdisser, 2015; Almeida et al., 2018) and acoustic environment (Dein and Rüdisser, 2020). The present study provides the first application of *D2N* in environmental epidemiology research. Other researchers are encouraged to test it in relation to different health outcomes across bio-geographic/climatic zones and spatial scales. Although the high quality and precise land use data used in this study may have enabled the detection of associations between allergic symptoms and landscape pattern, *D2N* can be easily applied with commonly available land use data (e.g., CORINE). Even if the application of more detailed data resulted in a refined indicator estimation, proportionality and hence comparability is maintained if applied to less detailed data (Rüdisser et al., 2012).

This study is not without limitations. For one, its cross-sectional design hindered causal inference and we could not follow allergic symptoms trajectories during childhood (Burgess et al., 2008; Lovasi et al., 2013; Sbihi et al., 2015; Fuertes et al., 2016). Still, we reduced exposure misclassification by limiting the analysis to children who had lived at the same address since birth in sensitivity analyses. As expected, this strengthened our findings.

We preferred to align with more conservative views on imputing missing data in the outcome variables, as the pattern of missingness may depend on unobserved information to an unknown degree. Given the small percentage of missing values, we do not believe that they have had any materially-important impact on this study's findings.

We did not measure sensitization to aeroallergens with a skin prick test nor did we obtain allergen-specific IgE serum levels. Thus, we could not further check whether associations with allergic symptoms differed by atopic status. We also did not have medical records for allergy diagnoses. Instead, we relied on the ISAAC questionnaire to ascertain the child's allergic symptoms, which could have overestimated the prevalence of some allergic disorders (Kim et al., 2018). Nevertheless, ISAAC is a well-established screening tool in the pediatric population and has been routinely used in previous research (e.g., Fuertes et al., 2014a, b; Dadvand et al., 2014; Andrusaityte et al., 2016; Parmes et al., 2020). In addition, we used combinations of symptoms to define the outcomes (e.g., wheezing during/after exercise and dry cough at night), which has

been recommended to increase precision of self-reports (Lukrafka et al., 2010; Magzoub et al., 2017).

We had to rely on static exposure assessment, assuming that all of the exposure occurred in a circular buffer around child's home and school. We believe that in our case this was a reasonable assumption, given the limited mobility of children (Chambers et al., 2017). Further, we accounted for maternal-reported time spent outdoors by the child. It was not possible to use road networks to generate network buffers, because there are a lot of uncharted walkable paths in this rural mountainous area – paths that people regularly use. Given that questionnaire data were collected in 2004/2005, GPS tracking devices at that time were not considered. Relatedly, we did not have data on the exact plant species children were exposed to. Only two studies to-date have specifically accounted for the allergenic potential of specific tree species (Lai and Kontokosta, 2019; Markevych et al., 2020).

It may be argued that greenness and greyness indicators aligned with the survey year may not represent children's lifetime exposure (cf. Helbich, 2019). Unfortunately, we did not have detailed information on children's residential history. We partly controlled for that by excluding movers in sensitivity analyses. A previous study in this area found stable vegetation coverage over time (Dzhambov et al., 2019), and in our sample, NDVI at the time of the survey was highly correlated with NDVI during pregnancy ($r = 0.70$ to 0.85).

Relatedly, questionnaire data were from 2004/2005, while tree canopy cover was available at five-year intervals and CORINE at greater intervals (i.e., 1990, 2000, 2006, 2012, 2018, etc.). As we investigated the long-term influence of residential and school environment, we used land cover data from the closest year preceding questionnaire data collection. We chose 2000 tree canopy cover to be commensurate with the 2000 land cover. Of note, in this relatively short time period, only minor land cover changes occurred (Hinojosa et al., 2019).

This study looked at the effect of spatial gradients in naturalness across an area with high background vegetation coverage. Therefore, it is unclear whether our findings can be directly transferred to other settings, which warrants replication in urban areas.

Finally, we only tested single mediation by air pollution, traffic noise and time spent outdoors. However, there are multiple other pathways of interest, like plant species diversity and microbial soil diversity, which should be investigated as they operate together to generate health effects.

5. Conclusions

Our findings suggest that for 8–12 year old children in alpine settings, residing in places with lower naturalness and higher greyness contributes to asthma and especially to allergic rhinitis. Greater residential greenness showed inconsistent results but overall displayed a tendency to be inversely associated with allergic rhinitis and asthma. The composite landscape index, Distance to Nature (*D2N*) captured the association between landscape characteristics and asthma in a more consistent and comprehensive manner than other measures (i.e., NDVI). Analyses with complex landscape characteristics and in children without a family history of allergic diseases provide a better understanding of who can profit from these alpine natural landscapes. Gene-environment interactions may clarify some of the heterogeneous findings in the extant literature.

Credit author statement

Angel M. Dzhambov: Conceptualization, Methodology, Software, Formal analysis; Investigation; Writing - original draft; Writing - review & editing, Peter Lercher: Conceptualization, Methodology; Investigation; Writing - original draft; Writing - review & editing; Project administration, Johannes Rüdisser: Methodology; Investigation; Writing - original draft; Writing - review & editing; Visualization, Matthew H.E. M. Browning: Methodology; Investigation; Writing - original draft;

Writing - review & editing, Iana Markevych: Methodology; Investigation; Writing - original draft; Writing - review & editing; Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We want to thank first the inhabitants of the Lower Inn and Wipp valleys. Our thanks also go to the Austrian Ministry of Science and Transportation for funding the framework of the Environmental Health Impact Assessment (EHIA), the government of the Tyrol region for providing GIS data and informational support from the BEG (Brenner Eisenbahn Gesellschaft).

The BBT survey got support from the BBT company within the framework of a legally required EHIA through EU-support. The noise mapping was done by INTEC, Ghent, and the air pollution assessment by an Italian-Austrian consortium. Finally, we thank the large EHIA-teams in both studies, who did the fieldwork.

Iana Markevych is supported from the “NeuroSmog: Determining the impact of air pollution on the developing brain” (Nr. POIR.04.04.00-1763/18-00) which is implemented as part of the TEAM-NET programme of the Foundation for Polish Science, co-financed from EU resources, obtained from the European Regional Development Fund under the Smart Growth Operational Programme. Johannes Rüdiger is a member of the Interdisciplinary Research Center ‘Ecology of the Alpine Region’ within the research area ‘Mountain Regions’ at the University of Innsbruck.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2020.110456>.

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Supplemental material

Allergic symptoms in association with naturalness, greenness, and greyness: A cross-sectional study in schoolchildren in the Alps

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Table S1. Study population characteristics – extended table

Characteristics	N	%	Mean ± SD	Median ± IQR	Range
Socio-demographics					
Age [years]	1251	100	9.36 ± 0.65	9.35 ± 1.02	7.96-12.04
Male	623	49.8	.	.	.
Maternal education					
Basic	279	22.3	.	.	.
Skilled labor	396	31.7	.	.	.
Vocational	287	22.9	.	.	.
A-level	247	19.7	.	.	.
Allergic symptoms^a					
Current asthma	250	20.0	.	.	.
Ever allergic rhinitis	311	24.9	.	.	.
Ever eczema	258	20.6	.	.	.
Ever asthma	265	21.2	.	.	.
Early biological exposome					
Low birth weight	77	6.2	.	.	.
Pregnancy smoking	146	11.7	.	.	.
Cumulative risk 1 st year ^b					
0 factors	849	67.9	.	.	.
1 factor	320	25.6	.	.	.
2 factors	36	2.9	.	.	.
3 factors	5	0.4	.	.	.
Breast feeding [months]	1222	97.7	5.39 ± 5.63	4.00 ± 7.00	0-51
Family history of atopy	421	33.7	.	.	.
Green months during pregnancy	1251	100	4.60 ± 1.26	5.00 ± 3.00	3.00-6.00
Living conditions					
Crowding [people/rooms]	1231	98.4	1.09 ± 0.41	1.00 ± 0.45	0.17-4.00
Pet in the home during 1 st year	221	17.7	.	.	.
Mould/dampness	314	25.1	.	.	.
Living on a farm	168	13.4	.	.	.
Presence of domestic garden	1175	93.9	.	.	.
Distance to nature					
<i>D2N</i> _{100-m}	1249	99.8	0.30 ± 0.15	0.27 ± 0.21	0.04-0.94
<i>D2N</i> _{500-m}	1249	99.8	0.23 ± 0.12	0.21 ± 0.13	0.04-0.77
<i>D2N</i> _{1000-m}	1249	99.8	0.18 ± 0.10	0.16 ± 0.10	0.04-0.62
Residential greenness					
NDVI _{100-m}	1251	100	0.43 ± 0.13	0.43 ± 0.20	0.06-0.74
NDVI _{500-m}	1251	100	0.50 ± 0.07	0.50 ± 0.10	0.27-0.68
NDVI _{1000-m}	1251	100	0.51 ± 0.05	0.52 ± 0.06	0.38-0.63
Tree cover _{100-m} [%]	1251	100	32.40 ± 9.85	31.01 ± 14.28	14.58-60.00
Tree cover _{500-m} [%]	1251	100	34.68 ± 9.32	33.92 ± 14.04	15.76-59.85

Tree cover _{1000-m} [%]	1251	100	39.24 ± 8.64	39.47 ± 13.11	21.36-60.42
Agricultural cover _{100-m}	1251	100	0.28 ± 0.37	0.06 ± 0.51	0.00-1.00
Agricultural cover _{500-m}	1251	100	0.36 ± 0.21	0.36 ± 0.28	0.00-1.00
Agricultural cover _{1000-m}	1251	100	0.35 ± 0.14	0.34 ± 0.19	0.00-0.90
Residential greyness					
Imperviousness _{100-m} [%]	1251	100	28.97 ± 21.83	26.31 ± 38.02	0.00-90.26
Imperviousness _{500-m} [%]	1251	100	15.97 ± 13.66	12.74 ± 20.40	0.00-59.32
Imperviousness _{1000-m} [%]	1251	100	10.38 ± 9.25	7.62 ± 11.80	0.00-40.33
Industrial cover _{100-m}	1251	100	0.66 ± 0.40	0.86 ± 0.64	0.00-1.00
Industrial cover _{500-m}	1251	100	0.40 ± 0.27	0.40 ± 0.41	0.00-1.00
Industrial cover _{1000-m}	1251	100	0.25 ± 0.18	0.24 ± 0.26	0.00-0.78
Putative mediators					
L _{den} [dBA(A)]	1223	97.8	52.51 ± 11.32	53.00 ± 15.20	30.00-79.79
NO ₂ [µg/m ³]	1137	90.9	15.97 ± 9.34	12.68 ± 8.80	8.00-66.55
Time spent outdoors [> 6 hrs/d]	530	42.4	.	.	.
School exposure					
<i>D2N</i> _{100-m}	1249	99.8	0.40 ± 0.14	0.42 ± 0.19	0.10-0.65
NDVI _{100-m}	1251	100	0.34 ± 0.11	0.34 ± 0.09	0.06-0.64
Tree cover _{100-m} [%]	1251	100	27.8 ± 27.91	26.66 ± 10.91	17.46-48.75
Agricultural cover _{100-m}	1251	100	0.15 ± 0.28	0.00 ± 0.14	0.00-1.00
Region					
Inn valley	251	20.1	.		
Wipp valley north (side)	326	26.1	.	.	.
Wipp valley south (side)	133	10.6	.	.	.
Wipp valley north (main)	326	26.1	.	.	.
Wipp valley south (main)	215	17.2	.	.	.

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

^a Current asthma = wheezing, dry cough at night and/or medication against asthma in the last 12 months; Ever allergic rhinitis = hay fever or non-cold-related sneezing, runny or blocked nose at any time in the past; Ever eczema = eczema or an itchy rash for at least six months; Ever asthma = asthma or wheezing/whistling at any time in the past.

^b Cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life.

Table S2. Study population characteristics stratified by presence of allergic symptoms

Characteristics	Current asthma (N = 250, 20.0%)			Ever allergic rhinitis (N = 311, 24.9%)			Ever eczema (N = 258, 20.6%)			Ever asthma (N = 265, 21.2%)		
	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value
Age [years] (Mean, SD)	9.37 (0.66)	9.29 (0.63)	0.087	9.37 (0.65)	9.33 (0.67)	0.449	9.33 (0.66)	9.43 (0.65)	0.044	9.36 (0.66)	9.36 (0.65)	0.969
Gender (N, %)			1.000			0.035			0.291			0.126
Female	486 (50.2)	125 (50.0)		468 (51.8)	139 (44.7)		471 (50.8)	121 (46.9)		483 (51.2)	121 (45.7)	
Male	482 (49.8)	125 (50.0)		436 (48.2)	172 (55.3)		456 (29.2)	137 (53.1)		460 (48.8)	144 (54.3)	
Maternal education (N, %)			0.648			0.610			0.258			0.390
Basic	221 (23.5)	51 (21.1)		204 (23.3)	65 (21.3)		216 (24.0)	55 (22.0)		209 (22.8)	55 (21.6)	
Skilled labor	306 (32.6)	82 (33.9)		291 (33.2)	94 (30.8)		302 (33.5)	72 (28.8)		307 (33.5)	78 (30.6)	
Vocational	216 (23.0)	63 (26.0)		204 (23.3)	80 (26.2)		206 (22.9)	70 (28.0)		207 (22.6)	71 (27.8)	
A-level	196 (20.9)	46 (19.0)		177 (20.2)	66 (21.6)		177 (19.6)	53 (21.2)		193 (21.1)	51 (20.0)	
Low birth weight (N, %)			0.077			0.682			0.774			0.316
No	893 (94.3)	223 (91.0)		829 (93.9)	285 (93.1)		844 (93.4)	241 (94.1)		867 (94.0)	241 (92.3)	
Yes	54 (5.7)	22 (9.0)		54 (6.1)	21 (6.9)		60 (6.6)	15 (5.9)		55 (6.0)	20 (7.7)	
Pregnancy smoking (N, %)			0.375			1.000			0.376			0.271
No	846 (88.7)	213 (86.6)		782 (88.0)	271 (88.0)		804 (87.9)	228 (90.1)		828 (89.0)	224 (86.5)	
Yes	108 (11.3)	33 (13.4)		107 (12.0)	37 (12.0)		111 (12.1)	25 (9.9)		102 (11.0)	35 (13.5)	
Cumulative risk in 1st year (N, %)			< 0.001			0.932			0.715			<0.001
0 factors	690 (73.2)	143 (59.1)		620 (70.5)	208 (68.9)		634 (70.3)	175 (70.0)		683 (74.3)	149 (58.0)	
1 factor	231 (24.5)	80 (33.1)		230 (26.2)	84 (27.8)		238 (26.4)	65 (26.0)		219 (23.8)	87 (33.9)	
2 factors	20 (2.1)	16 (6.6)		25 (2.8)	9 (3.0)		27 (3.0)	8 (3.2)		14 (1.5)	20 (7.8)	
3 factors	2 (0.2)	3 (1.2)		4 (0.5)	1 (0.3)		3 (0.3)	2 (0.8)		3 (0.3)	1 (0.4)	
Breast feeding [months] (Median, IQR)	4.00 (6.00)	4.00 (7.00)	0.706	4.00 (7.00)	4.00 (6.00)	0.475	4.00 (7.00)	4.00 (6.00)	0.878	4.00 (7.00)	4.00 (7.00)	0.297
Family history of atopy (N, %)			<0.001			<0.001			<0.001			<0.001
No	607 (66.6)	124 (52.8)		599 (70.3)	129 (44.2)		605 (69.5)	113 (45.7)		596 (67.5)	126 (50.2)	
Yes	304 (33.4)	111 (47.2)		253 (29.7)	163 (55.8)		265 (30.5)	134 (54.3)		287 (32.5)	125 (49.8)	
Crowding [people/rooms] (Median, IQR)	1.00 (0.45)	1.00 (0.45)	0.664	1.00 (0.45)	1.00 (0.50)	0.796	1.00 (0.45)	1.00 (0.45)	0.711	1.00 (0.45)	1.00 (0.45)	0.804
Pet in the home during 1st year (N, %)			0.412			0.714			0.302			0.162
No	763 (81.7)	222 (84.1)		752 (81.7)	211 (82.7)		730 (81.3)	259 (84.1)		783 (81.4)	211 (85.4)	
Yes	171 (18.3)	42 (15.9)		169 (18.3)	44 (17.3)		168 (18.7)	49 (15.9)		179 (18.6)	36 (14.6)	
Mold/dampness (N, %)			0.004			0.199			0.061			0.007
No	738 (76.6)	169 (67.6)		682 (75.6)	223 (71.9)		705 (76.4)	182 (70.5)		712 (75.9)	179 (67.5)	
Yes	225 (23.4)	81 (32.4)		220 (24.4)	87 (71.9)		218 (23.6)	76 (29.5)		226 (24.1)	86 (32.5)	
Living on a farm (N, %)			0.021			<0.001			1.000			0.414
No	823 (85.6)	226 (91.1)		750 (83.6)	295 (94.9)		796 (86.4)	223 (86.4)		805 (86.0)	233 (88.3)	
Yes	139 (14.4)	22 (8.9)		147 (16.4)	16 (5.1)		125 (13.6)	35 (13.6)		131 (14.0)	31 (11.7)	
Domestic garden (N, %)			0.033			0.359			0.418			0.107
No	228 (23.7)	76 (30.4)		217 (24.1)	82 (26.7)		239 (26.0)	60 (23.3)		223 (23.8)	76 (28.8)	
Yes	733 (76.3)	174 (69.6)		684 (75.9)	225 (73.3)		682 (74.0)	197 (76.7)		714 (76.2)	188 (71.2)	
Time outdoors (N, %)			0.030			0.022			0.389			0.436
≤ 6 hrs/d	515 (54.8)	154 (62.6)		479 (54.3)	187 (61.9)		502 (55.5)	147 (58.6)		510 (55.4)	151 (58.3)	
> 6 hrs/d	425 (45.2)	92 (37.4)		403 (45.7)	115 (38.1)		403 (44.5)	104 (41.4)		410 (44.6)	108 (41.7)	
Region (N, %)			0.452			0.295			0.326			0.823
Inn valley	187 (19.3)	57 (22.8)		180 (19.9)	63 (20.3)		194 (20.9)	43 (16.7)		183 (19.4)	59 (22.3)	
Wipp valley north (side)	262 (27.1)	60 (24.0)		232 (25.7)	88 (28.3)		251 (27.1)	63 (24.4)		246 (26.1)	70 (26.4)	
Wipp valley south (side)	105 (10.8)	24 (9.6)		102 (11.3)	22 (7.1)		95 (10.2)	31 (12.0)		99 (10.5)	29 (10.9)	
Wipp valley north (main)	243 (25.1)	71 (28.4)		233 (25.8)	84 (27.0)		228 (24.6)	75 (29.1)		248 (26.3)	64 (24.2)	
Wipp valley south (main)	171 (17.7)	38 (15.2)		157 (17.4)	54 (17.4)		159 (17.2)	46 (17.8)		167 (17.7)	43 (16.2)	

NDVI_{500-m} (Mean, SD)	0.50 (0.07)	0.49 (0.07)	0.071	0.50 (0.07)	0.49 (0.08)	0.042	0.50 (0.07)	0.50 (0.07)	0.794	0.50 (0.08)	0.49 (0.07)	0.174
Tree cover_{500-m} [%] (Mean, SD)	34.90 (9.36)	34.00 (9.15)	0.172	34.95 (9.26)	33.96 (9.60)	0.112	34.46 (9.35)	35.84 (9.26)	0.035	34.74 (9.38)	34.43 (9.07)	0.626
D2N_{500-m} (mean, SD)	0.23 (0.12)	0.24 (0.13)	0.140	0.22 (0.12)	0.24 (0.14)	0.009	0.23 (0.12)	0.22 (0.12)	0.087	0.23 (0.12)	0.23 (0.12)	0.473
Agricultural cover_{500-m} (Mean, SD)	0.36 (0.22)	0.35 (0.20)	0.535	0.36 (0.21)	0.34 (0.21)	0.053	0.36 (0.22)	0.37 (0.20)	0.713	0.36 (0.22)	0.35 (0.20)	0.350
Imperviousness_{500-m} [%] (Median, IQR)	12.34 (20.43)	17.36 (20.54)	0.136	12.73 (20.73)	14.52 (20.29)	0.500	13.07 (20.55)	11.69 (19.01)	0.368	12.41 (20.91)	14.76 (18.91)	0.119
Industrial cover_{500-m} (median, IQR)	0.39 (0.42)	0.44 (0.36)	0.055	0.39 (0.43)	0.45 (0.40)	0.017	0.41 (0.40)	0.37 (0.42)	0.197	0.40 (0.43)	0.44 (0.40)	0.211
L_{den} [dBA(A)] (Mean, SD)	52.31 (11.34)	53.31 (11.04)	0.2012	52.50 (11.39)	52.66 (11.09)	0.835	52.55 (11.44)	52.23 (10.98)	0.692	52.69 (11.41)	52.02 (10.78)	0.383
NO₂ [µg/m³] (Mean, SD)	15.57 (8.84)	17.55 (11.09)	0.014	15.96 (9.63)	16.10 (8.26)	0.812	15.94 (9.49)	16.18 (9.14)	0.718	15.78 (9.13)	16.60 (9.85)	0.247

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

Table S3. Correlations between the environmental and mediator variables in the study

Variables	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
1. <i>D2N</i> _{500-m}	1	-.708*	-.750*	-.393*	.837*	.784*	.595*	-.462*	-.586*	-.287*	.094*	.537*	-.213*	-.134*
2. NDVI _{500-m}		1	.508*	.654*	-.904*	-.790*	-.515*	.605*	.512*	.297*	-.184*	-.425*	.257*	.106*
3. Tree cover _{500-m}			1	.090*	-.718*	-.683*	-.426*	.434*	.630*	.326*	-.083*	-.356*	.218*	.105*
4. Agricultural cover _{500-m}				1	-.557*	-.714*	-.526*	.352*	.349*	.448*	.101*	-.116*	.137*	.146*
5. Imperviousness _{500-m}					1	.874*	.562*	-.636*	-.634*	-.376*	.240*	.484*	-.297*	-.139*
6. Industrial cover _{500-m}						1	.635*	-.511*	-.632*	-.552*	.036	.342*	-.233*	-.179*
7. <i>D2N</i> _{100-m} school							1	-.557*	-.759*	-.543*	-.082*	.190*	-.138*	-.148*
8. NDVI _{100-m} school								1	.645*	.411*	-.278*	-.254*	.275*	.095*
9. Tree cover _{100-m} school									1	.579*	-.074*	-.336*	.216*	.124*
10. Agricultural cover _{100-m} school										1	-.009	-.139*	.100*	.161*
11. L _{den}											1	.422*	-.103*	-.025
12. NO ₂												1	-.076*	-.108*
13. Domestic garden													1	.104*
14. Time outdoors														1

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

*Correlation is significant at the 0.05 level (2-tailed).

Table S4. Associations between landscape characteristics and allergic symptoms – extended table

		Current asthma		Ever allergic rhinitis		Ever eczema		Ever asthma	
		N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Exposure indicator (analytic sample)									
Distance to nature (D2N)		1112		1110		1082		1104	
	100-m		1.14 (0.90, 1.44)		1.23 (0.99, 1.53)		0.90 (0.71, 1.14)		1.07 (0.85, 1.35)
	500-m		1.21 (0.98, 1.48)		1.32 (1.09, 1.60)*		0.91 (0.74, 1.13)		1.13 (0.92, 1.38)
	1000-m		1.23 (0.96, 1.59)		1.38 (1.10, 1.74)*		0.95 (0.73, 1.22)		1.16 (0.91, 1.49)
Residential greenness		1112		1110		1082		1104	
	NDVI								
	100-m		0.87 (0.67, 1.13)		0.92 (0.73, 1.16)		0.96 (0.75, 1.23)		0.79 (0.61, 1.01)
	500-m		0.80 (0.63, 1.02)		0.83 (0.67, 1.03)		0.95 (0.75, 1.21)		0.81 (0.64, 1.03)
	1000-m		0.83 (0.66, 1.06)		0.83 (0.67, 1.03)		1.00 (0.80, 1.26)		0.85 (0.68, 1.07)
Tree cover									
	100-m		0.83 (0.65, 1.06)		0.87 (0.70, 1.08)		1.20 (0.96, 1.50)		0.93 (0.73, 1.17)
	500-m		0.86 (0.66, 1.12)		0.86 (0.68, 1.09)		1.22 (0.95, 1.56)		0.94 (0.73, 1.22)
	1000-m		0.95 (0.72, 1.27)		0.84 (0.65, 1.09)		1.13 (0.86, 1.48)		0.95 (0.72, 1.26)
Agricultural cover									
	100-m		0.91 (0.71, 1.15)		0.85 (0.68, 1.06)		0.95 (0.75, 1.19)		0.87 (0.69, 1.10)
	500-m		1.01 (0.81, 1.28)		0.88 (0.71, 1.08)		0.96 (0.77, 1.20)		0.92 (0.73, 1.15)
	1000-m		1.00 (0.80, 1.26)		0.88 (0.71, 1.08)		1.07 (0.85, 1.34)		0.95 (0.76, 1.19)
Domestic garden		1107	0.72 (0.51, 1.01)	1105	0.85 (0.62, 1.17)	1077	1.08 (0.76, 1.52)	1099	0.71 (0.51, 1.00)
Residential greyness		1112		1110		1082		1104	
	Imperviousness								
	100-m		1.12 (0.84, 1.49)		1.15 (0.89, 1.49)		0.96 (0.72, 1.27)		1.34 (1.02, 1.77)*
	500-m		1.30 (0.99, 1.71)		1.35 (1.05, 1.73)*		0.93 (0.71, 1.23)		1.24 (0.95, 1.63)
	1000-m		1.19 (0.92, 1.54)		1.38 (1.08, 1.75)*		0.91 (0.70, 1.17)		1.17 (0.91, 1.51)

	Industrial cover								
	100-m		1.22 (0.92, 1.61)		1.30 (1.00, 1.67)*		1.08 (0.83, 1.41)		1.24 (0.94, 1.64)
	500-m		1.25 (0.95, 1.64)		1.33 (1.04, 1.71)*		0.88 (0.67, 1.15)		1.24 (0.94, 1.62)
	1000-m		1.16 (0.88, 1.53)		1.37 (1.06, 1.76)*		0.84 (0.64, 1.11)		1.15 (0.88, 1.52)
Putative mediators									
	L _{den}	1087	1.10 (0.95, 1.29)	1086	1.02 (0.89, 1.18)	1058	0.93 (0.80, 1.08)	1081	0.92 (0.79, 1.08)
	NO ₂	1020	1.57 (1.22, 2.03)*	1016	1.02 (0.79, 1.32)	991	1.02 (0.78, 1.33)	1009	1.23 (0.94, 1.61)
	Time outdoors	1083	0.70 (0.51, 0.97)*	1082	0.72 (0.54, 0.97)*	1056	0.93 (0.68, 1.27)	1078	0.86 (0.63, 1.17)
School exposure in 100-m buffer									
	D2N	1111		1109		1081		1104	
	D2N		1.01 (0.78, 1.31)		1.16 (0.92, 1.48)		1.02 (0.79, 1.32)		0.98 (0.76, 1.27)
	NDVI		0.96 (0.82, 1.12)		0.86 (0.74, 0.99)*		0.96 (0.83, 1.12)		0.99 (0.85, 1.15)
	Tree cover		0.89 (0.69, 1.15)		0.73 (0.57, 0.94)*		0.92 (0.72, 1.17)		0.93 (0.73, 1.19)
	Agricultural cover		0.96 (0.87, 1.06)		0.93 (0.85, 1.02)		0.96 (0.88, 1.05)		1.01 (0.92, 1.10)

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover), per 10 dB(A) (L_{den}), per 10 µg/m³ (NO₂), for presence vs. absence of a domestic garden and for spending > 6 hrs/day outdoors.

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S5. Minimally-adjusted associations between landscape characteristics and allergic symptoms

	Current asthma	Ever allergic rhinitis	Ever eczema	Ever asthma
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure indicator (analytic sample)				
Distance to nature				
D2N (1181/1181/1151/1171)				
100-m	1.16 (0.93, 1.45)	1.26 (1.03, 1.55)*	0.92 (0.73, 1.15)	1.01 (0.82, 1.26)
500-m	1.18 (0.97, 1.43)	1.32 (1.10, 1.58)*	0.92 (0.75, 1.12)	1.04 (0.86, 1.26)
1000-m	1.20 (0.95, 1.52)	1.38 (1.10, 1.72)*	0.93 (0.73, 1.18)	1.07 (0.85, 1.34)
Residential greenness				
NDVI (1181/1181/1151/1171)				
100-m	0.87 (0.68, 1.11)	0.89 (0.71, 1.11)	0.97 (0.76, 1.24)	0.80 (0.63, 1.02)
500-m	0.80 (0.63, 1.00)	0.81 (0.65, 0.99)*	0.96 (0.76, 1.21)	0.87 (0.70, 1.09)
1000-m	0.83 (0.67, 1.04)	0.81 (0.66, 0.99)*	1.01 (0.81, 1.26)	0.90 (0.73, 1.12)
Tree cover (1181/1181/1151/1171)				
100-m	0.82 (0.65, 1.04)	0.86 (0.70, 1.06)	1.19 (0.96, 1.48)	0.97 (0.78, 1.21)
500-m	0.84 (0.66, 1.08)	0.86 (0.68, 1.08)	1.22 (0.96, 1.55)	0.98 (0.77, 1.24)
1000-m	0.93 (0.71, 1.22)	0.84 (0.65, 1.07)	1.15 (0.89, 1.49)	0.98 (0.76, 1.28)
Agricultural cover (1181/1181/1151/1171)				
100-m	0.91 (0.72, 1.14)	0.84 (0.68, 1.04)	0.94 (0.75, 1.17)	0.88 (0.70, .11)
500-m	0.98 (0.79, 1.23)	0.86 (0.70, 1.05)	0.94 (0.75, 1.16)	0.93 (0.75, 1.16)
1000-m	0.99 (0.80, 1.23)	0.88 (0.71, 1.07)	1.02 (0.82, 1.27)	0.97 (0.79, 1.20)
Domestic garden (1176/1176/1146/1166)	0.69 (0.50, 0.96)*	0.85 (0.63, 1.16)	1.13 (0.81, 1.59)	0.74 (0.54, 1.02)
Residential greyness				
Imperviousness (1181/1181/1151/1171)				
100-m	1.14 (0.87, 1.50)	1.18 (0.92, 1.51)	0.95 (0.73, 1.25)	1.32 (1.01, 1.71)*
500-m	1.30 (1.00, 1.68)*	1.37 (1.08, 1.74)*	0.93 (0.71, 1.21)	1.15 (0.89, 1.49)
1000-m	1.21 (0.95, 1.54)	1.39 (1.11, 1.74)*	0.90 (0.71, 1.16)	1.11 (0.88, .41)

	Industrial cover (1181/1181/1151/1171)				
	100-m	1.24 (0.95, 1.63)	1.31 (1.02, 1.68)*	1.09 (0.84, 1.41)	1.22 (0.93, .59)
	500-m	1.29 (0.99, 1.67)	1.36 (1.07, 1.73)*	0.91 (0.70, 1.17)	1.16 (0.90, 1.49)
	1000-m	1.19 (0.92, 1.55)	1.38 (1.08, 1.76)*	0.85 (0.66, 1.11)	1.09 (0.85, 1.41)
	Putative mediators				
	L _{den} (1155/1156/1126/1148)	1.07 (0.92, 1.24)	1.02 (0.89, 1.17)	0.92 (0.80, 1.07)	0.93 (0.80, 1.08)
	NO ₂ (1078/1077/1050/1068)	1.46 (1.15, 1.86)*	1.04 (0.81, 1.32)	1.02 (0.79, 1.32)	1.20 (0.94, 1.54)
	Time outdoors (> 6 hrs/d) (1150/1151/1123/1143)	0.73 (0.54, 1.00)*	0.74 (0.55, 0.98)*	0.91 (0.67, 1.23)	0.91 (0.68, 1.23)
	School exposure in 100-m buffer				
	D2N (1179/1179/1149/1171)	1.03 (0.80, 1.32)	1.19 (0.95, 1.50)	1.00 (0.78, 1.29)	0.95 (.75, 1.21)
	NDVI (1179/1179/1149/1171)	0.93 (0.81, 1.08)	0.85 (0.74, 0.97)*	0.96 (0.83, 1.11)	0.98 (0.85, 1.13)
	Tree cover (1179/1179/1149/1171)	0.87 (0.68, 1.12)	0.75 (0.59, 1.08)*	0.95 (0.75, 1.21)	0.96 (0.76, 1.22)
	Agricultural cover (1179/1179/1149/1171)	0.95 (0.86, 1.04)	0.93 (0.85, 1.02)	0.97 (0.89, 1.06)	1.01 (0.93, 1.10)

Abbreviations: *D2N* – Distance to nature, *L_{den}* – total day-evening-night noise level; *NDVI* – Normalized Difference Vegetation Index, *NO₂* – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, *NDVI*, tree cover, agricultural cover, imperviousness and industrial cover), per 10 dB(A) (*L_{den}*), per 10 µg/m³ (*NO₂*), for presence vs. absence of a domestic garden and for spending > 6 hrs/day outdoors.

The models are adjusted for age, gender, maternal education, and geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S6. Fully-adjusted associations between landscape characteristics and allergic symptoms

	Current asthma	Ever allergic rhinitis	Ever eczema	Ever asthma
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Exposure indicator (analytic sample)				
Distance to nature				
D2N (1087/1084/1059/1079)				
100-m	1.11 (0.87, 1.42)	1.17 (0.93, 1.46)	0.90 (0.71, 1.15)	1.08 (0.85, 1.37)
500-m	1.17 (0.95, 1.45)	1.23 (1.01, 1.50)*	0.91 (0.73, 1.13)	1.13 (0.92, 1.40)
1000-m	1.19 (0.92, 1.55)	1.28 (1.00, 1.63)*	0.94 (0.72, 1.22)	1.17 (0.91, 1.51)
Residential greenness				
NDVI (1087/1084/1059/1079)				
100-m	0.90 (0.69, 1.18)	1.04 (0.81, 1.33)	0.96 (0.74, 1.24)	0.78 (0.60, 1.01)
500-m	0.84 (0.65, 1.09)	0.94 (0.74, 1.18)	0.96 (0.74, 1.23)	0.82 (0.64, 1.05)
1000-m	0.88 (0.69, 1.12)	0.92 (0.73, 1.15)	1.00 (0.79, 1.27)	0.86 (0.68, 1.08)
Tree cover (1087/1084/1059/1079)				
100-m	0.87 (0.68, 1.12)	0.94 (0.75, 1.17)	1.21 (0.96, 1.53)	0.93 (0.73, 1.18)
500-m	0.91 (0.69, 1.19)	0.93 (0.73, 1.20)	1.23 (0.95, 1.59)	0.94 (0.73, 1.23)
1000-m	1.00 (0.75, 1.35)	0.90 (0.68, 1.18)	1.13 (0.85, 1.49)	0.94 (0.71, 1.26)
Agricultural cover (1087/1084/1059/1079)				
100-m	0.96 (0.74, 1.23)	0.97 (0.76, 1.22)	0.92 (0.72, 1.17)	0.86 (0.67, 1.10)
500-m	1.06 (0.84, 1.35)	0.96 (0.77, 1.20)	0.93 (0.74, 1.17)	0.92 (0.73, 1.16)
1000-m	1.02 (0.81, 1.30)	0.92 (0.74, 1.15)	1.04 (0.83, 1.31)	0.97 (0.77, 1.22)
Domestic garden (1085/1082/1057/1077)	0.77 (0.54, 1.10)	0.92 (0.66, 1.28)	1.09 (0.76, 1.56)	0.74 (0.52, 1.05)
Residential greyness				
Imperviousness (1087/1084/1059/1079)				
100-m	1.05 (0.78, 1.41)	1.02 (0.78, 1.35)	0.93 (0.69, 1.25)	1.36 (1.02, 1.82)*
500-m	1.21 (0.90, 1.62)	1.17 (0.89, 1.53)	0.92 (0.68, 1.23)	1.24 (0.93, 1.64)
1000-m	1.09 (0.83, 1.44)	1.21 (0.94, 1.56)	0.91 (0.69, 1.19)	1.17 (0.90, 1.54)

Industrial cover (1087/1084/1059/1079)				
100-m	1.14 (0.84, 1.53)	1.10 (0.84, 1.45)	1.10 (0.83, 1.45)	1.25 (0.93, 1.68)
500-m	1.15 (0.86, 1.54)	1.14 (0.87, 1.49)	0.88 (0.66, 1.16)	1.23 (0.93, 1.64)
1000-m	1.06 (0.79, 1.43)	1.19 (0.91, 1.57)	0.84 (0.63, 1.12)	1.15 (0.86, 1.54)
Putative mediators				
L _{den} (1063/1061/1036/1057)	1.07 (0.91, 1.25)	0.99 (0.85, 1.14)	0.91 (0.78, 1.06)	0.91 (0.78, 1.06)
NO ₂ (997/992/970/986)	1.57 (1.20, 2.04)*	0.98 (0.75, 1.29)	1.00 (0.76, 1.32)	1.23 (0.94, 1.62)
Time outdoors (> 6 hrs/d) (1059/1057/1034/1054)	0.76 (0.55, 1.06)	0.78 (0.57, 1.05)	0.92 (0.67, 1.27)	0.90 (0.65, 1.24)
School exposure in 100-m buffer				
D2N (1087/1084/1059/1079)	0.98 (0.75, 1.28)	1.07 (0.83, 1.37)	1.03 (0.79, 1.34)	0.96 (0.74, 1.25)
NDVI (1087/1084/1059/1079)	0.99 (0.85, 1.16)	0.90 (0.78, 1.05)	0.96 (0.82, 1.12)	1.01 (0.86, 1.17)
Tree cover (1087/1084/1059/1079)	0.92 (0.71, 1.20)	0.81 (0.63, 1.03)	0.90 (0.70, 1.17)	0.96 (0.74, 1.23)
Agricultural cover (1087/1084/1059/1079)	0.97 (0.88, 1.08)	0.94 (0.86, 1.04)	0.94 (0.85, 1.04)	1.02 (0.93, 1.12)

Abbreviations: D2N – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (D2N, NDVI, tree cover, agricultural cover, imperviousness and industrial cover), per 10 dB(A) (L_{den}), per 10 µg/m³ (NO₂), for presence vs. absence of a domestic garden and for spending > 6 hrs/day outdoors.

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region, living on a farm, crowding, mould/dampness, pet in the first year of life.

*Estimate is statistically significant at the p < 0.05 level.

Table S7. Mediation of the association between landscape characteristics and current asthma symptoms

		Conditional direct effect	Natural indirect effect	Total effect
Greenness/greyness indicator (analytic sample)		OR (95% CI)	OR (95% CI)	OR (95% CI)
NDVI _{500-m}				
	NO ₂ (1044)	0.90 (0.69, 1.20)	0.91 (0.84, 0.96)*	0.82 (0.63, 1.09)
	L _{den} (1116)	0.85 (0.67, 1.09)	1.00 (0.97, 1.00)	0.85 (0.67, 1.08)
	Time spent outdoors (1113)	0.84 (0.66, 1.07)	0.99 (0.98, 1.00)	0.83 (0.65, 1.06)
Tree cover _{500-m}				
	NO ₂ (1044)	0.93 (0.71, 1.23)	0.94 (0.89, 0.98)*	0.88 (0.68, 1.16)
	L _{den} (1116)	0.89 (0.68, 1.15)	1.01 (1.00, 1.03)	0.90 (0.68, 1.16)
	Time spent outdoors (1113)	0.90 (0.70, 1.19)	0.98 (0.96, 1.00)*	0.89 (0.69, 1.17)
D2N _{500-m}				
	NO ₂ (1044)	1.10 (0.86, 1.40)	1.08 (1.03, 1.15)*	1.19 (0.94, 1.50)
	L _{den} (1116)	1.12 (0.93, 1.40)	1.00 (1.00, 1.02)	1.13 (0.93, 1.39)
	Time spent outdoors (1113)	1.12 (0.93, 1.39)	1.01 (1.00, 1.05)	1.14 (0.94, 1.42)
Agricultural cover _{500-m}				
	NO ₂ (1044)	1.04 (0.81, 1.35)	0.98 (0.94, 1.00)	1.01 (0.80, 1.32)
	L _{den} (1116)	1.03 (0.83, 1.32)	1.02 (1.00, 1.05)	1.05 (0.84, 1.33)
	Time spent outdoors (1113)	1.03 (0.81, 1.28)	1.00 (0.97, 1.01)	1.03 (0.81, 1.28)
Imperviousness _{500-m}				
	NO ₂ (1044)	1.14 (0.80, 1.56)	1.14 (1.06, 1.25)*	1.30 (0.92, 1.79)
	L _{den} (1116)	1.18 (0.88, 1.57)	1.02 (0.98, 1.06)	1.21 (0.90, 1.57)
	Time spent outdoors (1113)	1.22 (0.93, 1.58)	1.02 (1.00, 1.06)*	1.24 (0.95, 1.64)
Industrial cover _{500-m}				
	NO ₂ (1044)	1.15 (0.85, 1.54)	1.10 (1.03, 1.17)*	1.26 (0.92, 1.68)
	L _{den} (1116)	1.18 (0.88, 1.55)	1.00 (0.97, 1.01)	1.18 (0.87, 1.88)
	Time spent outdoors (1113)	1.17 (0.89, 1.53)	1.02 (1.00, 1.06)	1.19 (0.92, 1.56)

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover).

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, and geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S8. Mediation of the association between landscape characteristics and ever allergic rhinitis symptoms

	Conditional direct effect	Natural indirect effect	Total effect
Greenness/greyness indicator (analytic sample)	OR (95% CI)	OR (95% CI)	OR (95% CI)
NDVI _{500-m}			
NO ₂ (1038)	0.85 (0.66, 1.10)	1.01 (0.96, 1.07)	0.85 (0.67, 1.09)
L _{den} (1112)	0.81 (0.66, 1.05)	1.00 (0.98, 1.00)	0.81 (0.66, 1.05)
Time spent outdoors (1109)	0.90 (0.71, 1.14)	0.99 (0.98, 1.00)	0.89 (0.70, 1.13)
Tree cover _{500-m}			
NO ₂ (1038)	0.88 (0.67, 1.12)	1.00 (0.97, 1.03)	0.88 (0.67, 1.12)
L _{den} (1112)	0.84 (0.65, 1.07)	1.00 (1.00, 1.02)	0.84 (0.65, 1.07)
Time spent outdoors (1109)	0.92 (0.71, 1.19)	0.99 (0.97, 1.00)	0.91 (0.70, 1.16)
D2N _{500-m}			
NO ₂ (1038)	1.33 (1.06, 1.61)*	0.99 (0.94, 1.03)	1.31 (1.05, 1.60)*
L _{den} (1112)	1.35 (1.09, 1.63)*	1.00 (0.99, 1.01)	1.35 (1.09, 1.64)*
Time spent outdoors (1109)	1.24 (1.00, 1.51)	1.01 (1.00, 1.04)	1.26 (1.02, 1.54)*
Agricultural cover _{500-m}			
NO ₂ (1038)	0.91 (0.72, 1.15)	1.00 (0.99, 1.02)	0.91 (0.71, 1.15)
L _{den} (1112)	0.87 (0.71, 1.07)	1.00 (0.98, 1.03)	0.88 (0.71, 1.07)
Time spent outdoors (1109)	0.92 (0.75, 1.13)	1.00 (0.98, 1.01)	0.92 (0.74, 1.13)
Imperviousness _{500-m}			
NO ₂ (1038)	1.35 (1.01, 1.82)*	0.98 (0.91, 1.05)	1.33 (1.01, 1.80)*
L _{den} (1112)	1.39 (1.06, 1.83)*	1.00 (0.97, 1.04)	1.39 (1.07, 1.80)*
Time spent outdoors (1109)	1.24 (0.97, 1.59)	1.02 (1.00, 1.05)	1.26 (0.99, 1.63)
Industrial cover _{500-m}			
NO ₂ (1038)	1.32 (0.98, 1.69)	0.99 (0.94, 1.04)	1.31 (0.97, 1.65)
L _{den} (1112)	1.36 (1.04, 1.80)*	1.00 (0.98, 1.01)	1.36 (1.04, 1.80)*
Time spent outdoors (1109)	1.23 (0.94, 1.58)	1.02 (1.00, 1.06)*	1.25 (0.97, 1.62)

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover).

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, and geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S9. Mediation of the association between landscape characteristics and ever eczema symptoms

		Conditional direct effect	Natural indirect effect	Total effect
Greenness/greyness indicator (analytic sample)		OR (95% CI)	OR (95% CI)	OR (95% CI)
NDVI _{500-m}				
	NO ₂ (1013)	0.81 (0.63, 1.11)	1.00 (0.95, 1.07)	0.82 (0.64, 1.10)
	L _{den} (1084)	0.90 (0.71, 1.17)	1.00 (1.00, 1.02)	0.90 (0.71, 1.18)
	Time spent outdoors (1083)	0.97 (0.75, 1.24)	1.00 (0.99, 1.00)	0.97 (0.75, 1.23)
Tree cover _{500-m}				
	NO ₂ (1013)	1.13 (0.88, 1.42)	0.99 (0.96, 1.03)	1.12 (0.87, 1.40)
	L _{den} (1084)	1.17 (0.91, 1.47)	1.00 (0.98, 1.00)	1.16 (0.90, 1.46)
	Time spent outdoors (1083)	1.24 (0.96, 1.62)	1.00 (0.97, 1.01)	1.23 (0.95, 1.61)
D2N _{500-m}				
	NO ₂ (1013)	0.95 (0.75, 1.20)	1.01 (0.96, 1.06)	0.96 (0.77, 1.20)
	L _{den} (1084)	0.92 (0.74, 1.18)	1.00 (0.98, 1.00)	0.92 (0.74, 1.18)
	Time spent outdoors (1083)	0.89 (0.69, 1.11)	1.00 (1.00, 1.03)	0.89 (0.71, 1.13)
Agricultural cover _{500-m}				
	NO ₂ (1013)	0.85 (0.67, 1.07)	1.00 (0.98, 1.01)	0.85 (0.67, 1.07)
	L _{den} (1084)	0.95 (0.74, 1.16)	0.99 (0.96, 1.01)	0.94 (0.74, 1.15)
	Time spent outdoors (1083)	0.99 (0.78, 1.25)	1.00 (0.98, 1.00)	0.99 (0.77, 1.24)
Imperviousness _{500-m}				
	NO ₂ (1013)	1.12 (0.79, 1.52)	1.00 (0.92, 1.09)	1.12 (0.81, 1.50)
	L _{den} (1084)	1.01 (0.75, 1.36)	0.98 (0.94, 1.02)	0.99 (0.74, 1.32)
	Time spent outdoors (1083)	0.91 (0.69, 1.23)	1.01 (0.99, 1.04)	0.92 (0.69, 1.24)
Industrial cover _{500-m}				
	NO ₂ (1013)	1.02 (0.75, 1.38)	1.01 (0.95, 1.07)	1.03 (0.77, 1.38)
	L _{den} (1084)	0.94 (0.71, 1.24)	1.00 (0.99, 1.02)	0.94 (0.71, 1.25)
	Time spent outdoors (1083)	0.86 (0.65, 1.14)	1.01 (0.99, 1.04)	0.87 (0.66, 1.15)

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover).

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, and geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S10. Mediation of the association between landscape characteristics and ever asthma symptoms

		Conditional direct effect	Natural indirect effect	Total effect
Greenness/greyness indicator (analytic sample)		OR (95% CI)	OR (95% CI)	OR (95% CI)
NDVI _{500-m}				
	NO ₂ (1035)	0.79 (0.62, 1.03)	0.96 (0.91, 1.02)	0.77 (0.60, 0.98)*
	L _{den} (1010)	0.82 (0.65, 1.02)	1.00 (1.00, 1.03)	0.82 (0.64, 1.03)
	Time spent outdoors (1108)	0.82 (0.66, 1.06)	0.65 (0.98, 1.00)	1.05 (0.66, 1.06)
Tree cover _{500-m}				
	NO ₂ (1035)	0.96 (0.73, 1.25)	0.97 (0.93, 1.00)	0.93 (0.71, 1.21)
	L _{den} (1010)	0.96 (0.74, 1.25)	1.00 (0.98, 1.00)	0.96 (0.74, 1.25)
	Time spent outdoors (1108)	0.99 (0.76, 1.29)	0.99 (0.97, 1.01)	0.98 (0.76, 1.27)
D2N _{500-m}				
	NO ₂ (1035)	1.14 (0.90, 1.42)	1.04 (0.99, 1.10)	1.18 (0.93, 1.47)
	L _{den} (1010)	1.10 (0.89, 1.31)	1.00 (0.98, 1.00)	1.10 (0.89, 1.31)
	Time spent outdoors (1108)	1.06 (0.87, 1.30)	1.01 (0.99, 1.03)	1.07 (0.88, 1.31)
Agricultural cover _{500-m}				
	NO ₂ (1035)	0.92 (0.71, 1.16)	0.99 (0.96, 1.00)	0.91 (0.71, 1.17)
	L _{den} (1010)	0.92 (0.74, 1.16)	0.99 (0.97, 1.01)	0.91 (0.73, 1.15)
	Time spent outdoors (1108)	0.92 (0.75, 1.14)	1.00 (0.98, 1.00)	0.92 (0.74, 1.14)
Imperviousness _{500-m}				
	NO ₂ (1035)	1.28 (0.92, 1.76)	1.05 (0.96, 1.15)	1.34 (0.96, 1.81)
	L _{den} (1010)	1.27 (0.95, 1.67)	0.98 (0.94, 1.01)	1.24 (0.92, 1.62)
	Time spent outdoors (1108)	1.20 (0.92, 1.53)	1.01 (0.99, 1.04)	1.20 (0.93, 1.53)
Industrial cover _{500-m}				
	NO ₂ (1035)	1.26 (0.95, 1.68)	1.04 (0.98, 1.11)	1.31 (0.98, 1.73)
	L _{den} (1010)	1.23 (0.93, 1.66)	1.00 (0.99, 1.02)	1.23 (0.92, 1.65)
	Time spent outdoors (1108)	1.18 (0.88, 1.56)	1.01 (0.99, 1.04)	1.19 (0.88, 1.56)

Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover).

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, and geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S11. Stratified associations between residential distance to nature ($D2N_{500-m}$) and allergic symptoms and effect modification by child's characteristics

Effect modifier	N	Current asthma	p-int	N	Ever allergic rhinitis	p-int	N	Ever eczema	p-int	N	Ever asthma	p-int.
Gender			0.329			0.905			0.001			0.230
Female	554	1.08 (0.80, 1.46)		552	1.37 (1.03, 1.82)*		538	1.25 (0.93, 1.70)		546	1.21 (0.88, 1.67)	
Male	556	1.38 (1.02, 1.86)*		556	1.30 (1.00, 1.70)*		544	0.62 (0.45, 0.85)*		556	1.08 (0.82, 1.42)	
Maternal education			0.538			0.821			0.008			0.113
Basic	255	1.32 (0.78, 2.25)		250	1.73 (1.06, 2.81)*		252	1.48 (0.86, 2.55)		248	1.35 (0.79, 2.32)	
Skilled	366	1.09 (0.76, 1.55)		364	1.19 (0.85, 1.66)		353	0.57 (0.36, 0.90)*		364	1.13 (0.79, 1.62)	
Vocational	263	1.12 (0.76, 1.66)		265	1.28 (0.88, 1.85)		257	1.09 (0.74, 1.60)		262	1.11 (0.76, 1.62)	
A-level	224	1.82 (1.05, 3.15)		215	1.28 (0.82, 2.01)		214	0.83 (0.51, 1.35)		213	1.26 (0.74, 2.13)	
Crowding			0.845			0.535			0.895			0.005
< 1 (people/rooms)	334	1.64 (1.11, 2.41)*		335	1.70 (1.21, 2.39)*		328	1.27 (0.85, 1.91)		334	1.13 (0.76, 1.69)	
≥ 1 (people/rooms)	765	1.09 (0.85, 1.41)		760	1.16 (0.91, 1.48)		743	0.77 (0.59, 1.00)		758	1.20 (0.93, 1.54)	
Breast feeding			0.353			0.243			0.061			0.633
< 4 months	520	1.41 (1.04, 1.91)*		514	1.13 (0.85, 1.49)		503	0.78 (0.57, 1.08)		516	1.17 (0.86, 1.59)	
≥ 4 months	592	1.13 (0.84, 1.52)		596	1.51 (1.15, 1.98)*		579	1.02 (0.76, 1.37)		588	1.10 (0.83, 1.46)	
Pet (1st year)			0.755			0.514			0.391			0.590
No	905	1.09 (0.87, 1.37)		901	1.29 (1.04, 1.60)*		876	0.87 (0.69, 1.10)		897	1.17 (0.93, 1.46)	
Yes	201	2.50 (1.29, 4.85)*		198	1.23 (0.74, 2.05)		199	1.21 (0.68, 2.18)		200	0.99 (0.59, 1.65)	
Mould/dampness			0.901			0.201			0.756			0.418
No	828	1.22 (0.96, 1.55)		825	1.27 (1.02, 1.58)*		807	0.93 (0.73, 1.19)		813	1.11 (0.87, 1.40)	
Yes	281	1.30 (0.84, 1.99)		279	1.50 (0.99, 2.29)		270	0.83 (0.51, 1.34)		287	1.31 (0.86, 1.99)	
Living on a farm			0.138			0.654			0.859			0.066
No	961	1.13 (0.91, 1.41)		958	1.23 (1.00, 1.50)		934	0.88 (0.71, 1.10)		951	1.09 (0.88, 1.36)	
Yes	140	1.41 (0.57, 3.44)		129	1.65 (0.56, 4.82)		137	1.15 (0.42, 3.15)		143	1.67 (0.79, 3.55)	
Time outdoors			0.993			0.359			0.155			0.639
≤ 6hrs/d	607	1.13 (0.88, 1.47)		607	1.22 (0.95, 1.56)		590	0.94 (0.72, 1.23)		601	1.13 (0.87, 1.46)	

> 6hrs/d	476	1.30 (0.89, 1.89)		475	1.35 (0.97, 1.88)		466	0.84 (0.59, 1.23)		477	1.12 (0.79, 1.59)	
Region (valley)			0.154			0.478			0.146			0.324
Inntal	210	1.47 (1.06, 2.03)*		211	1.31 (0.99, 1.74)		208	0.83 (0.59, 1.17)		212	1.11 (0.80, 1.54)	
Wipp valley north (main)	298	0.79 (0.46, 1.37)		299	0.90 (0.53, 1.50)		288	0.58 (0.33, 1.01)		296	1.13 (0.62, 2.06)	
Wipp valley north (side)	293	1.73 (1.05, 2.87)*		287	1.42 (0.91, 2.21)		286	1.04 (0.63, 1.74)		288	1.69 (1.06, 2.70)*	
Wipp valley south (main)	189	1.10 (0.62, 1.95)		191	1.78 (1.09, 2.92)*		185	1.47 (0.87, 2.48)		191	0.97 (0.56, 1.67)	
Wipp valley south (side)	116	0.87 (0.09, 8.24)		109	1.12 (0.11, 10.85)		114	1.86 (0.25, 13.91)		115	2.61 (0.36, 19.01)	
NO₂			0.741			0.845				0.219		0.176
< 12.68 µg/m ³	503	1.17 (0.77, 1.78)		507	1.25 (0.86, 1.81)		496	0.80 (0.52, 1.23)		503	1.46 (0.99, 2.17)	
≥ 12.68 µg/m ³	507	1.15 (0.88, 1.51)		507	1.29 (0.99, 1.67)		493	1.04 (0.80, 1.35)		505	1.10 (0.83, 1.45)	

Abbreviations: *D2N* – Distance to nature, NO₂ – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase in distance to nature.

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.

Table S12. Subgroup associations between landscape characteristics and allergic symptoms

	Current asthma	Ever allergic rhinitis	Ever eczema	Ever asthma
Exposure indicator (analytic sample)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Subgroup: Same home address since birth			
Distance to nature				
<i>D2N</i> _{500-m} (638/636/619/625)	1.16 (0.89, 1.51)	1.24 (0.96, 1.59)	0.79 (0.60, 1.04)	1.27 (0.97, 1.66)
Residential greenness				
NDVI _{500-m} (638/636/619/625)	0.78 (0.57, 1.07)	0.84 (0.63, 1.12)	1.20 (0.87, 1.66)	0.81 (0.59, 1.10)
Tree cover _{500-m} (638/636/619/625)	0.98 (0.69, 1.39)	0.99 (0.73, 1.34)	1.69 (1.21, 2.35)*	0.97 (0.69, 1.37)
Agricultural cover _{500-m} (638/636/619/625)	0.96 (0.71, 1.29)	0.92 (0.70, 1.21)	1.06 (0.79, 1.42)	0.86 (0.63, 1.16)
Garden (636/632/617/623)	0.59 (0.38, 0.91)*	0.83 (0.55, 1.24)	1.14 (0.74, 1.78)	0.63 (0.40, 0.97)*
Residential greyness				
Imperviousness _{500-m} (638/636/619/625)	1.27 (0.90, 1.81)	1.32 (0.96, 1.82)	0.67 (0.47, 0.97)*	1.32 (0.93, 1.88)
Industrial cover _{500-m} (638/636/619/625)	1.16 (0.81, 1.66)	1.13 (0.82, 1.57)	0.65 (0.46, 0.93)*	1.28 (0.89, 1.83)
Putative mediators				
<i>L</i> _{den} (614/613/596/605)	1.13 (0.92, 1.39)	1.10 (0.92, 1.32)	1.01 (0.83, 1.22)	0.96 (0.79, 1.18)
NO ₂ (570/567/552/559)	1.58 (1.14, 2.19)*	0.85 (0.60, 1.21)	0.93 (0.66, 1.31)	1.16 (0.82, 1.65)
	Subgroup: No Family history of asthma/allergic rhinitis/eczema			
Distance to nature				
<i>D2N</i> _{500-m} (663/660/648/653)	1.33 (1.00, 1.77)	1.29 (0.98, 1.70)	0.77 (0.56, 1.07)	1.35 (1.02, 1.79)*
Residential greenness				
NDVI _{500-m} (663/660/648/653)	0.60 (0.43, 0.84)*	0.80 (0.57, 1.11)	0.91 (0.64, 1.31)	0.65 (0.47, 0.91)*
TC _{500-m} (663/660/648/653)	0.75 (0.52, 1.08)	0.85 (0.60, 1.21)	1.31 (0.91, 1.88)	0.84 (.59, 1.21)
Agricultural cover _{500-m} (663/660/648/653)	0.83 (0.60, 1.14)	0.91 (0.67, 1.24)	0.86 (0.62, 1.19)	0.82 (0.60, 1.12)
Garden (657/654/648/653)	0.67 (0.41, 1.09)	1.25 (0.74, 2.08)	1.18 (0.69, 2.02)	0.79 (0.48, 1.28)
Residential greyness				
Imperviousness _{500-m} (663/660/648/653)	1.79 (1.22, 2.63)*	1.40 (0.97, 2.03)	0.88 (0.58, 1.33)	1.63 (1.12, 2.36)*

Industrial cover _{500-m} (663/660/648/653)	1.78 (1.19, 2.64)*	1.28 (0.88, 1.86)	0.87 (0.58, 1.29)	1.56 (1.06, 2.29)*
Putative mediators				
L _{den} (648/646/638/644)	1.09 (0.89, 1.35)	1.07 (0.87, 1.32)	0.94 (0.76, 1.16)	0.88 (0.72, 1.09)
NO ₂ (605/602/593/598)	1.50 (1.06, 2.13)*	1.02 (0.70, 1.47)	0.69 (0.44, 1.06)	1.21 (0.83, 1.76)

Note. Abbreviations: *D2N* – Distance to nature, L_{den} – total day-evening-night noise level; NDVI – Normalized Difference Vegetation Index, NO₂ – nitrogen dioxide.

Coefficients are odds ratios (ORs) with their 95% confidence intervals (CIs). Effect sizes are presented per one interquartile range increase (*D2N*, NDVI, tree cover, agricultural cover, imperviousness and industrial cover), per 10 dB(A) (L_{den}), per 10 µg/m³ (NO₂), for presence vs. absence of a domestic garden and for spending > 6 hrs/day vs. ≤ 6 hrs/day outdoors.

The models are adjusted for age, gender, maternal education, low birth weight, maternal smoking during pregnancy, duration of breastfeeding, cumulative risk of secondhand smoking/pneumonia/bronchitis in the 1st year of life, number of green months during pregnancy, geographic region.

*Estimate is statistically significant at the $p < 0.05$ level.