Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: evidence from 9 European cohorts.

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Abstract

Introduction

Recent research focused on the interaction between land cover and the development of allergic and respiratory disease has provided conflicting results and the underlying mechanisms are not fully understood. In particular, green space, which confers an overall positive impact on general health, may be significantly contributing to adverse respiratory health outcomes. This study evaluates associations between surrounding residential land cover (green, grey, agricultural and blue space), including type of forest cover (deciduous, coniferous and mixed), and childhood allergic and respiratory diseases.

Methods

Data from 8,063 children, aged 3-14 years, were obtained from nine European population-based studies participating in the HEALS project. Land-cover exposures within a 500 m buffer centred on each child's residential address were computed using data from the Coordination of Information on the Environment (CORINE) program. The associations of allergic and respiratory symptoms (wheeze, asthma, allergic rhinitis and eczema) with land coverage were estimated for each study using logistic regression models, adjusted for sex, age, body mass index, maternal education, parental smoking, and parental history of allergy. Finally, the pooled effects across studies were estimated using meta-analyses.

Results

In the pooled analyses, a 10% increase in green space coverage was significantly associated with a 5.9% to 13.0% increase in the odds of wheezing, asthma, and allergic rhinitis, but not eczema. A trend of an inverse relationship between agricultural space and respiratory symptoms was observed, but did not reach statistical significance. In secondary analyses, children living in areas with surrounding coniferous forests had significantly greater odds of reporting wheezing, asthma and allergic rhinitis.

Conclusion

Our results provide further evidence that exposure to green space is associated with increased respiratory disease in children. Additionally, our findings suggest that coniferous forests might be associated with wheezing, asthma and allergic rhinitis. Additional studies evaluating both the type of green space, and also the use of green space, in relation to respiratory conditions should be conducted in order to clarify the underlying mechanisms behind associated adverse impacts.

Key words: Land Cover, Green Space, Forests, Allergy, Asthma

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Ethical Approval:

Ethical approval was not requested for this secondary analysis of pooled data from previous studies. In each of the original studies, ethical approval was obtained for each centre from the appropriate ethics committee, see the Online Supplement. All procedures have conformed to the principles embodied in the Declaration of Helsinki.

1. Introduction

As urban and suburban environments continue to develop worldwide, understanding the health impacts resulting from different land cover classes is increasingly pertinent. Recent epidemiological studies have evaluated the health impacts of specific land cover types, including urban/grey space, green space, and proximity to agricultural areas or water bodies (blue spaces) (Markevych et al., 2017; Twohig-Bennett and Jones, 2018; van den Berg et al., 2015). Overall, positive health associations have been found with increasing green space exposure, ranging from mental health issues (Engemann et al., 2019) to reductions in diastolic blood pressure, salivary cortisol and heart rate, to decreases in incidence of diabetes, all-cause and cardiovascular mortality (Alcock et al., 2014; Twohig-Bennett and Jones, 2018).

Whether and how green space is related to allergic and respiratory health, however, is unresolved in the literature. While green space may mitigate pollution levels by removing pollutants from the air or by limiting the space available for emission sources, it is also a source of pollens, aggravating allergies and increasing particulate matter counts (van den Bosch and Nieuwenhuijsen, 2017). Forests and soil are a huge source and reservoir of biogenic volatile organic compounds, which can also be detrimental to respiratory health (Gibbs, 2019; Goldstein and Galbally, 2007). Knowledge on how these spaces affect human health is crucial in addressing the increasing worldwide prevalence of asthma and allergies and to direct urban and community planning for prevention (De Marco et al., 2012; Ruokolainen, 2017).

Children are particularly susceptible to the adverse impacts of environmental exposures. At certain early stages of life, when immune and respiratory systems are still developing, exposure to environmental toxins can lead to irreversible health damage (Thurston et al., 2017). Compared to adults, children are generally more active, spend more time outdoors and breathe in more air than adults do in proportion to their weight. Further, allergic and respiratory diseases in paediatric populations have increased in recent decades along with urbanisation (Asher et al., 2006; Pesce et al., 2015).

Studies on the effect of land cover on allergic and respiratory health are increasing, but their results can be contradictory and meta-analyses are often not conclusive. This is presumably due to demographic and/or geographical differences (Fuertes et al., 2014), as well as methodological differences in the assessment of the exposures between cohorts and in the definition of the outcomes across cohorts and studies (Lambert et al., 2017).

The CORINE Land Cover (CLC) is a European wide standardised land cover map spanning a large time scale managed by the European Environmental Agency. It has advantages in that it combines geo-spatial environmental information from national databases and satellite images into 44 land cover classes describing various types of artificial surfaces, agricultural land, forests, wetlands and water bodies (Kosztra et al., 2017).

The aim of this study was to use CLC to estimate the percentage of green, blue, agricultural and grey spaces surrounding the residence of 8,063 children, aged 3-14 years, from nine European cohorts to evaluate associations between these four broad land cover types and six indicators of allergy and respiratory health during childhood, including asthma, wheezing, allergic rhinitis and eczema. After individual cohorts were evaluated, meta-analyses were conducted to calculate the pooled effect across studies. As details on the type of vegetation may be crucial in understanding the actual impacts these spaces have on allergy and respiratory outcomes (Gernes et al., 2019), a secondary analysis was also conducted to further investigate the effects of different types of tree cover on health outcomes by taking advantage of the distinction CLC provides between coniferous and deciduous forests.

2. Materials and Methods

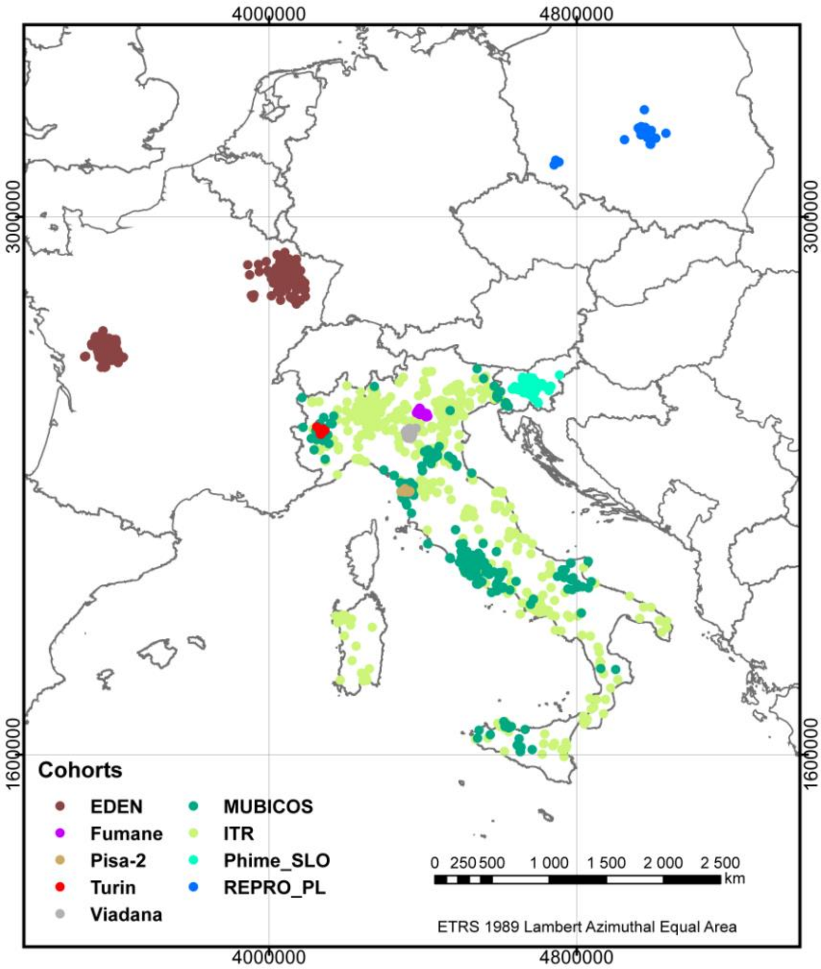
2.1 Study Population

The present study considers nine different cohorts across four European countries (Italy, France, Slovenia and Poland) that have contributed to the FP7 HEALS (Health and Environment-wide Associations based on Large population Surveys) project, aimed at assessing health-environment associations through an exposome approach (Wild, 2012). Detailed descriptions of the nine cohorts are reported in the Online Supplement (**Text S1**). From these, a subsample of 8,063 children with an age range of 3-14 years was selected based on the availability of information on wheezing, asthma and respiratory/allergic diseases and geocoded residential addresses:

1) 877 children (3-8 yrs) enrolled at birth in 2003-2006 and living in Nancy (Northeastern France) and Poitiers (Central France) from the EDEN study (Etude des Déterminantspré et post natals du développement et de la santé de l′Enfant) (Heude et al., 2016);
2) 748 schoolchildren (3-14 yrs) enrolled in 2009-2010 and living in the Province of Verona (Veneto, Northern Italy) from the Fumane & Mezzane di Sotto cross-sectional study (Marcon et al., 2014);
3) 1627 twins (age 3-14 yrs) enrolled in the Italian Twin Registry (ITR) study beginning in 2001 and living throughout Italy (Brescianini et al., 2013);
4) 274 twins (mean age 3 yrs) enrolled at birth in 2009 and living throughout Italy from the MUltipleBIrthCOhort (MUBICOS) study (Brescianini et al., 2013). MUBICOS is a subset of the ITR but not all ITR does not overlap this particular ITR sample.;
5) 167 children (age 7-8 years) recruited at birth in 2008-2009 from Ljubljana and its surroundings from the Slovenian study as part of the PHIME study (PHIME-SLO) (Miklavčič et al., 2011; Valent et al., 2013);
6) 135 children (8-14 yrs) enrolled in 1991-1993 and living in Pisa (Tuscany, Central Italy) from the Pisa-2 cross-sectional study (Maio et al., 2016; Nuvolone et al., 2011);
7) 78 children (7 yrs) enrolled during the first trimester of pregnancy in 2007 and living in Lodz district, Poland from the Polish Mother and Child Cohort (REPRO_PL) study(Polańska et al., 2016, 2011);
8) 393 schoolchildren (10-13 yrs) enrolled in 2003, followed-up in 2010 and living in Turin (Piedmont, Northern Italy) from the Turin cohort study (Piccioni et al., 2015);
9) 3764 schoolchildren (3-14 yrs) enrolled in 2006 and living in the district of Viadana (Mantua (Lombardy, Northern Italy) from the Viadana cross-sectional study (de Marco et al., 2010).

In each of the original studies, ethical approval was obtained from the local ethics committees. **Figure 1** shows the geographical distribution of the children included, differentiated by study.

Figure 1. Geographical distribution of the children included in the analyses differentiated by study.



2.2 Health outcomes and covariates

In all studies, data on health outcomes, as well as on potential confounders, were collected through parental questionnaires.

Children were classified as having:

- "*lifetime wheeze*" (wheeze) if children were reported to have ever had wheezing or whistling in the chest at any time in the past;
- "*current wheeze*" if the child had any wheezing in the last 12 months;
- "*lifetime asthma*" (asthma) if the child had asthma at any time in the past;
- "*current asthma*" if the child was currently taking medication for asthma and/or suffered an asthma attack in the last 12 months;
- "*lifetime allergic rhinitis*" if the child ever had any nasal allergy or hay fever at any time of the past;
- "*eczema*" if the child ever had an itchy rash on one or more parts of the skin which was coming and going or had been diagnosed with eczema.

The variables used in the assessment of the outcomes differed slightly across the studies. Details on the specific questions used in each study are described in the Online Supplement (**Table S1**). Child's age (years), sex, body mass index (BMI), parental history of allergy or asthma, parental smoking as a proxy of passive smoke exposure, maternal education ("high" if the mother has a high school diploma or higher qualification vs. “low”), used as proxy of socio-economic status, were considered as potential confounders in the models used to determine the associations between land covers and health outcomes.

2.3 Residential land cover

The participant’s residential addresses were geocoded, and re-projected into CLC’s Lambert equal area projection (Kosztra et al., 2017). The proportion of each CLC class surrounding each residential location was calculated by using buffer zones with four radii: 100 m, 300 m, 500 m, and 1000 m. The raster version of CLC with a pixel size of 100 m was used. Depending on the year of data collection for the specific cohort study, the nearest CLC layer was selected from the available 1990, 2000, 2006, 2012 or 2018 years: 1990 for Pisa-2, 2006 for Eden, Fumane, PHIME-SLO, Turin and Viadana, and 2012 for ITR, Mubicos and REPRO_PL. In the case of ITR, which is a twin registry and not a single study, 2012 was selected as it was the year closest to the visit dates of the children selected for this study. From the resulting proportions of original CLC classes, eight land cover features used in this study were calculated: percentages of green space, blue space, grey space, agricultural space, forest cover, coniferous forests, deciduous forests and mixed forests**.** Note that green spaces do not contain agricultural spaces. **Table 1** shows which original CLC classes make up each of the calculated exposure variables.

Table 1: Description of land cover features according to CORINE classification

Land cover feature	**CORINE code**	**Description**
Green space	1.4.1	Green urban areas
	1.4.2	Sport and leisure facilities
	3.1.1	Broad-leaved forest
	3.1.2	Coniferous forest
	3.1.3	Mixed forest
	3.2.1	Natural grassland
	3.2.2	Moors and heathland
	3.2.3	Sclerophyllous vegetation
	3.2.4	Transitional woodland/shrub
Grey space	1.1.1	Continuous urban fabric
	1.1.2	Discontinuous urban fabric
	1.2.1	Industrial or commercial units
	1.2.2	Road and rail networks and associated land
	1.2.3	Port areas
	1.2.4	Airports
	1.3.1	Mineral extraction sites
	1.3.2	Dump sites
	1.3.3	Construction sites
Blue space	5.1.1	Water courses
	5.1.2	Water bodies
	5.2.1	Coastal lagoons
	5.2.2	Estuaries
	5.2.3	Sea and ocean

Agricultural space	2.1.1	Non-irrigated arable land
	2.1.2	Permanently irrigated land
	2.1.3	Rice fields
	2.2.1	Vineyards
	2.2.2	Fruit trees and berry plantations
	2.2.3	Olive groves
	2.3.1	Pastures
	2.4.2	Complex cultivation patterns
	2.4.1	Annual crops associated with permanent crops
	2.4.3	Land occupied by agriculture, with areas of natural vegetation
	2.4.4	Agro-forestry areas
Forest	3.1.1	Broad-leaf forest
	3.1.2	Coniferous forest
	3.1.3	Mixed Forest
Broad-leaf forest	3.1.1	Broad-leaf forest
Coniferous forest	3.1.2	Coniferous forest
Mixed Forest	3.1.3	Mixed Forest

2.4 Statistical Analysis

To minimise bias from the heterogeneity of methodological protocols among studies, we used a two-stage approach for analysing individual participant data and calculating the pooled effect across studies (Fisher, 2015; Fuertes et al., 2016). In the first stage, associations of health outcomes with each of the land coverage indicators were estimated within each study using logistic regression models, adjusting for the potential confounders available in each study (sex, age, BMI, parental history of allergy, maternal education, parental smoking), and were expressed using odds ratios (OR) with corresponding 95% confidence intervals (95% CI). Cluster-robust standard errors were included in twin studies (i.e. ITR and Mubicos) to take into account any correlations between twin siblings. Land-cover main classes (i.e. green, grey, blue, and agricultural) were included in the model as continuous variables, and OR were estimated for a 10% increase of land coverage within a 500 m buffer. In each model, associations with health outcomes were estimated only in studies that had more than 10 cases in order to avoid data sparseness.

In the second stage, fixed-effects meta-analyses were performed on the estimates calculated for individual studies using the inverse-variance method and overall OR were calculated. Fixed-effects meta-analyses were adopted under the assumption that land cover features have the same effects on health outcomes across all studies. Random effects meta-analyses using the DerSimonian and Laird methods were performed when a significant heterogeneity across the studies emerged (Fisher, 2015).

As diagnosis of asthma can be difficult in very young children (Bacharier et al., 2008), analyses on current and lifetime asthma were restricted to children aged 6 and older.
A 0.05 significance level was adopted. All statistical analyses were performed with STATA 14.2.

2.5 Sensitivity Analyses

As health outcomes may have different clinical phenotypes that vary by age, we performed sensitivity analyses in which the children were stratified into three homogeneous age-groups (3-5; 6-10; 11-14 years), to further investigate whether land cover features were differently associated with the outcomes across these groups. To evaluate the potential interaction between sex and green space exposure, the models were also run separately for males and females. Additionally, to test the stability of the associations found in the main analyses, we performed two further sensitivity analyses using different indicators of exposure: 1) using a binary indicator of presence/absence of forests (any, coniferous, broad-leaf, mixed) within a 500 m buffer surrounding the children's home (i.e. 1=above vs. 0=below median) based on intra-study median coverage for each type of land-cover class; 2) adopting different distance buffers (100, 300 and 1000 m) for land-coverage around the home address. To check whether the inclusion of both twins in a pair might have over-weighted the Mubicos and ITR studies, we also performed a further sensitivity analysis where one child per pair was randomly excluded from the models.

Finally, the analyses of association of green, grey and agricultural space with respiratory outcomes were further adjusted for estimates of outdoor exposure to NO_2 (annual average concentrations) at the home addresses. These analyses were conducted for the EDEN and Viadana cohorts only (Heude et al., 2016; Marcon et al., 2014), since data on air pollution were not available for the other studies. For EDEN, a sensitivity analysis adjusted for PM_{10} exposure was also conducted. The methods for the exposure assessment and attribution are described in the Online Supplement (**Text S2**)."

3. Results

Overall, 8,063 children from the nine different studies across the four European countries (Italy, France, Slovenia and Poland) were geo-referenced and included in the analyses (**Figure 1**). The Viadana study contained the highest number of children (n=3,764). Females represented 47.7% of the overall sample, and the median age ranged from 3 years in the Mubicos study to 12 years in the Turin study. The children from the Pisa-2 study, which was the oldest study included (1991-1993), were the most exposed to passive smoking, but also those with lowest parental history of allergy and lowest parental education (**Table 2**). The distribution of respiratory and allergic health outcomes was significantly heterogeneous across studies. Children from the EDEN study in France, had the greatest prevalence for all six of the considered outcomes, with a prevalence of asthma and allergic rhinitis of 15.5% and 20.8%, respectively, and a prevalence of wheezing and eczema above 40%.

Table 2. Characteristics of the children included in the present study. *Data expressed as n (%) or median [range]. †children aged 6 and older. *Studies with <10 cases for one of the outcomes were excluded from the meta-analyses to avoid data sparseness.*

Survey	**EDEN**	**Fumane**	**ITR**	**Mubicos**	**Phime-SLO**	**Pisa-2**	**REPRO_PL**	**Turin**	**Viadana**
n	877	748	1,627	274	167	135	78	393	3,766
Country	France	Italy	Italy	Italy	Slovenia	Italy	Poland	Italy	Italy
Data collection	2003-2014	2010	2001-ongoing	2009-2014	2007-ongoing	1991-1993	2014-2019	2010	2006
Subject characteristics									
Age (years)	8 [3-8]	9 [3-14]	10 [3-14]	3 [-]	8 [7-8]	12 [8-14]	7 [-]	12 [10-13]	9 [3-14]
Female sex	445 (50.7%)	365 (48.8%)	805 (49.5%)	127 (46.4%)	84 (50.3%)	55 (40.7%)	44 (56.4%)	174 (44.3%)	1,745 (46.3%)
BMI (kg/m2)	15.6 [10.2-21.6]	17.0 [8.9-27.7]	17.4 [9.0-26.1]	11.3 [8.4-16.2]	15.8 [12.4-22.4]	19.1 [14.6-30.2]	15.9 [13.2-24.1]	18.3 [12.2-28.6]	17.2 [7.8-27.9]
Parental history of allergy	310 (35.4%)	254 (34.0%)	496 (30.5%)	42 (15.3%)	-	19 (14.1%)	12 (15.4%)	132 (33.6%)	846 (22.5%)
Passive smoking exposure	297 (33.9%)	351 (46.9%)	680 (41.8%)	38 (13.9%)	12 (7.2%)	75 (55.6%)	20 (25.6%)	94 (23.9%)	1,930 (51.3%)
Maternal education (high)	725 (82.7%)	484 (64.7%)	-	264 (96.4%)	119 (71.3%)	48 (35.6%)	72 (92.3%)	280 (71.2%)	1,941 (51.6%)
Outcomes									
Wheezing	362 (41.6%)	179 (24.5%)	494 (31.2%)	93 (33.9%)	-	20 (14.8%)	-	95 (24.7%)	874 (23.8%)
Current wheezing	100 (11.5%)	56 (7.6%)	135 (8.6%)	51 (18.6%)	-	-	-	23 (5.9%)	280 (7.6%)
Asthma†	110 (15.5%)	63 (9.8%)	129 (9.6%)	-	*7 (4.2%)**	14 (10.4%)	*8 (10.3%)**	46 (11.8%)	322 (6.9%)
Current asthma†	57 (8.0%)	43 (6.7%)	54 (4.0%)	-	-	*8 (5.9%)**	-	22 (6.0%)	136 (4.4%)
Allergic rhinitis	182 (20.8%)	78 (10.5%)	222 (13.9%)	-	-	19 (14.1%)	-	35 (9.0%)	303 (8.2%)
Eczema	361 (41.2%)	164 (22.0%)	238 (16.4%)	40 (17.8%)	37 (22.2%)	10 (7.4%)	21 (26.9%)	69 (17.6%)	801 (21.7%)

Land coverage around children's home

The distribution of land coverage around children's homes by buffer radius and study is shown in **Table 3**. In all studies, as the radius of the buffer around the children's home increased, the proportion of land covered by urban grey space decreased and, consequently, the proportion of green, blue and agricultural spaces increased. Within a 500 m radius buffer, the children recruited in the *Turin study* were the most exposed to urban grey space (land coverage: 94.4%), while the children from *Fumane* were the most exposed to green and agricultural space (12.6% and 59.6%, respectively). The children from the *Pisa-2 study* had no detectable green space within 500 m from their home, while those from *Turin* had an average proportion of agricultural space below 1%. In all studies, the proportion of blue space was extremely low, ranging from 0 to 1.1%. The correlation matrices showing the pairwise relation between different types of land cover and between different buffer sizes are shown, respectively, in **Fig S1** and **Fig S2** in the Online Supplement.

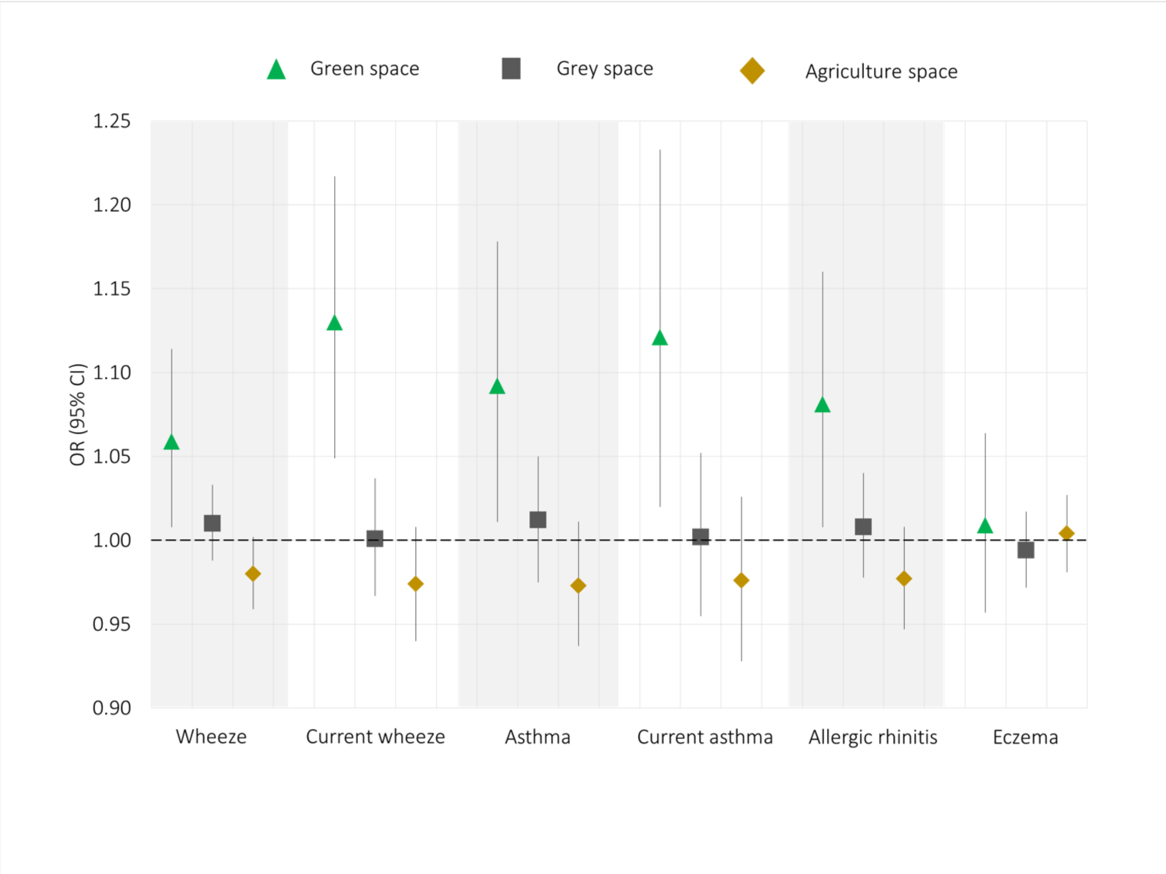
Table 3. Land coverage around children's home by buffer radius and study. *Data expressed as a percentage of land coverage, mean ± SD. Bold represents the chosen buffer for the primary analysis.*

Survey	EDEN	Fumane	ITR	Mubicos	Phime	Pisa-2	REPRO-PL	Turin	Viadana
n	877	748	1,627	274	167	135	78	393	3,766
Grey space									
<100 m	74.7±37.4	46.0±42.6	89.0±26.0	72.4±40.8	66.4±43.6	85.2±29.2	93.2±19.8	97.8±11.7	68.6±37.9
<300 m	67.6±32.4	36.7±31.6	81.6±26.5	67.8±36.8	61.7±38.6	76.5±24.9	87.4±21.6	96.3±11.6	56.7±30.0
<500 m	**60.0±31.8**	**27.7±22.7**	**76.4±26.5**	**62.5±34.7**	**55.5±36.3**	**66.9±22.1**	**83.1±22.5**	**94.4±12.3**	**45.7±25.3**
<1 km	47.2±32.2	14.2±11.9	67.0±26.9	52.0±32.3	44.1±33.7	52.6±20.3	76.1±21.3	90.3±12.0	41.7±30.4
Green space									
<100 m	2.5±12.4	6.2±18.0	1.7±10.1	5.5±21.5	6.6±20.7	0	1.7±7.6	1.4±8.4	1.0±6.2
<300 m	4.1±11.2	9.2±15.7	2.9±10.2	5.6±17.5	9.1±19.0	0	4.7±8.9	2.5±8.0	2.6±8.2
<500 m	**6.1±11.8**	**12.6±16.4**	**4.2±10.7**	**6.7±16.7**	**12.4±19.6**	**0**	**8.1±11.0**	**4.0±8.8**	**4.5±10.0**
<1 km	10.1±13.0	22.3±13.0	6.7±12.4	8.6±16.6	21.2±21.8	0.0±0.1	12.9±12.7	6.3±7.5	7.7±11.7
Blue space									
<100 m	0.5±5.1	0	0.1±1.5	0	0.2±1.8	0.6±3.8	0	0.4±5.0	0.1±2.2
<300 m	0.6±4.2	0	0.4±3.2	0.5±3.6	0.4±2.5	1.3±4.4	0	0.7±4.1	0.1±1.0
<500 m	**0.7±3.8**	**0.0±0.3**	**0.7±4.0**	**0.9±5.0**	**0.7±2.6**	**1.1±3.0**	**0**	**1.0±3.9**	**0.3±2.1**
<1 km	1.0±3.5	0.0±0.3	1.5±5.5	1.8±6.8	0.8±2.1	1.8±2.1	0	1.4±3.3	1.2±3.5
Agricultural space									
<100 m	22.3±35.8	47.8±41.4	9.0±23.6	22.1±37.2	26.8±39.5	14.2±28.9	5.0±18.8	0.4±5.0	30.3±37.8
<300 m	27.6±31.2	54.1±29.2	14.8±24.2	26.0±33.6	28.8±32.6	22.2±24.7	7.9±20.2	0.5±4.7	40.5±30.7
<500 m	**33.2±31.0**	**59.6±18.5**	**18.5±24.2**	**29.7±32.6**	**31.4±28.5**	**32.1±22.0**	**8.8±20.3**	**0.7±4.9**	**49.5±27.9**
<1 km	41.6±31.8	63.5±12.2	24.6±25.0	37.2±31.4	33.8±24.4	45.6±20.6	11.0±18.2	1.9±5.7	63.2±25.0

Associations of green, grey, blue and agricultural space exposure with allergic and respiratory health outcomes

In the primary analyses, we investigated the associations between residential surrounding land cover (e.g. green, grey, blue and agriculture spaces) within a 500 m radius buffer and six allergic and respiratory health outcomes. These analyses were done across nine participant studies, for a total of 24 meta-analyses (all forest plots are shown in the supporting material, **Figures S3-S6**). Overall, a median of 6,066 children (range: 4,814 to 6,806) and 5.5 studies (range: 4 to 9) were included in the meta-analyses, depending on the outcome and land cover variables. The meta-analysis results are summarised in **Table S2 in the Online Supplement**. The proportion of land covered by green space was significantly associated with increased odds of lifetime and current wheezing (+5.9% and +13.0%, respectively, per 10% increase in green-covered space), as well as with lifetime and current asthma and allergic rhinitis (+9.2%, +12.1%, and +8.1 respectively) (**Figure 2**). No significant associations were found between land cover classes and eczema. As significant heterogeneity between studies was found in the association between green space and lifetime wheezing, the analysis was repeated using random-effects meta-analysis. The results were consistent with the main analysis (OR=1.06, 95% CI:0.98-1.15).

Fig.2: Associations between land coverage within 500 m from children's home and allergic and respiratory outcomes. Odds ratios (OR with 95% confidence interval, CI) are estimated for a 10% increase of land covered by green, grey, or agricultural space.



The associations between green space and health outcomes were similar in males and females and across different ages groups (**Figure S7** and **Table S3** in the Online Supplement), indicating that there was no interaction between sex, age and exposure to green space on the considered outcomes. No statistically significant associations were found between exposures to urban grey and blue spaces in relation with any of the health outcomes tested in the meta-analyses. Agricultural space had a borderline negative association with lifetime wheezing, and was overall moderately protective, although not at statistically significant level, in all the considered respiratory outcomes.

The associations between green space exposure and respiratory outcomes were overall confirmed in all the sensitivity analyses: 1) When using a binary indicator for exposure based on intra-study median exposure (high vs. low exposure, **Table S4**); 2) when using different buffer radii (100m, 300m, and 1000m) (**Table S5**); and 3) when one of the twins from the twin cohorts (ITR and Mubicos) was randomly excluded from the models (**Table S6**). Further adjustment of the analyses for residential outdoor NO_2 levels (in Viadana and EDEN, Fig. S8) or PM_{10} (in EDEN only, data not shown) did not change the estimates for the associations between land cover features and health outcomes.

Associations between exposure to forests and allergic and respiratory outcomes

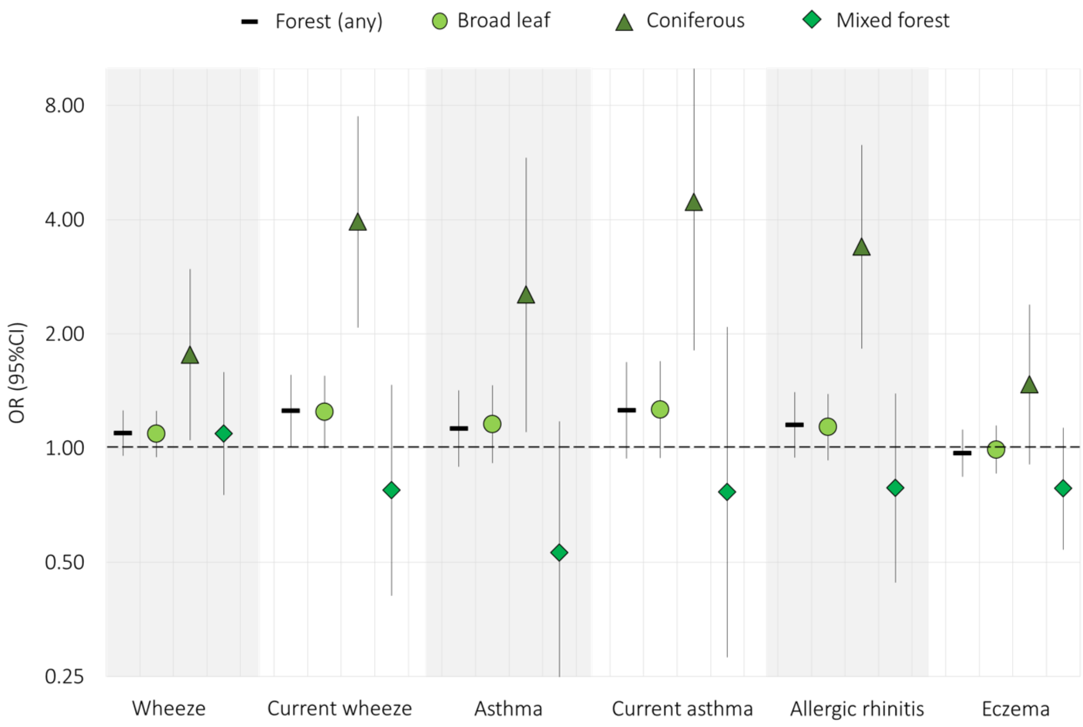
The presence of forests was investigated within 500 m from children's residential address and is presented in (**Table 4**). The children sampled in the Fumane study were the most exposed to forests (any type), while children from Pisa-2 were not exposed to forests within 500 m of their home. Children sampled in the Viadana and in the Turin studies, moreover, did not have any coniferous or mixed forests near home.

Table 4: Forest-covered land near children's residential home by study. Data indicate the number (%) of children who live within 500 m from a forest.

Survey	EDEN	Fumane	ITR	Mubicos	Phime	Pisa-2	REPRO-PL	Turin	Viadana
n	877	748	1,627	318	167	135	78	393	3,766
Forest (any)	270 (30.8)	483 (64.6)	178 (10.9)	50 (16.4)	89 (53.3)	0	6 (7.7)	12 (3.1)	1048 (27.9)
Broad-leaf forest	250 (28.5)	400 (53.5)	144 (8.9)	36 (13.1)	33 (19.8)	0	1 (1.3)	12 (3.1)	1048 (27.9)
Coniferous forest	14 (1.6)	32 (4.3)	22 (1.4)	6 (2.2)	19 (11.4)	0	2 (2.6)	0	0
Mixed forest	12 (1.4)	141 (18.9)	30 (1.8)	26 (9.5)	74 (44.3)	0	4 (5.1)	0	0

After adjusting meta-analyses for potential confounders, children with forests near their homes had a 26% greater odds of having current wheeze compared to those who lived further (OR=1.26; 95% CI: 1.01-1.56; $p=0.039$) (**Figure 3 and Table S7**). After separating between type of tree cover, children living close to a coniferous forest had greater odds of having current wheeze (OR=1.76; 95% CI:1.05-2.97), lifetime wheeze (OR=3.95; 95% CI: 2.08-7.49), current asthma (OR=4.45; 95%CI: 1.81-10.9), lifetime asthma (OR=2.54; 95% CI: 1.10-5.82) and allergic rhinitis (OR=3.39; 95% CI: 1.83-6.30) than those living further (all $p<0.05$). The detailed forest plots for the meta-analyses are displayed in **Figures S9-S12** in the Online Supplement.

Fig.3: Associations between proximity to forests and respiratory and allergic symptoms. Odds ratios (OR with 95% confidence interval, CI) indicate the risk for children who live within 500 m from a forest vs. those who live further.


Forest (any)
Broad leaf
Coniferous
Mixed forest
OR (95%CI)
8.00
4.00
2.00
1.00
0.50
0.25
Wheeze
Current wheeze
Asthma
Current asthma
Allergic rhinitis
Eczema

4. Discussion

Our study set out to investigate whether residential land cover was associated with the occurrence of respiratory and allergic symptoms in children. Meta-analyses were conducted based on data collected from nine paediatric cohorts from four European countries. We found that greater residential exposure to green space was associated with increased odds of wheezing and asthma (both current and lifetime) and lifetime allergic rhinitis, but not with eczema. Children living within a 500 m buffer including coniferous forests, in particular, were found to have odds of wheeze, asthma and allergic rhinitis that were 2- to 4-fold higher than those who did not. Grey (urban) and blue space were not associated with any of the studied outcomes, while agricultural space was moderately protective, although not at a statistically significant level, for all the respiratory outcomes.

Many studies investigating the impacts of green space have shown a largely beneficial influence on various health outcomes including wellbeing, diastolic blood pressure, salivary cortisol, heart rate, incidence of diabetes, all cause and cardiovascular mortality (Cilluffo et al., 2018; Engemann et al., 2019; Twohig-Bennett and Jones, 2018; van den Berg et al., 2015). Our results suggest that, contrary to impacts on these other health indicators, allergic and respiratory symptoms can increase with increased nearby green space and are consistent with many, but not all, studies focused on similar associations (Gernes et al., 2019; Lambert et al., 2017; Tischer et al., 2017).

Two questions arise: First, what underlying mechanisms cause green space to confer a negative impact to respiratory and allergic outcomes in children, and second, what is the reason for inconsistent results between studies?

Green spaces may be problematic for respiratory health because they are sources of VOC emissions, pollen, moulds, and aerosols, all of which have been shown to create allergies and respiratory health problems (Annesi-Maesano, 2013; Cecchi et al., 2018; Gibbs, 2019; Marchetti et al., 2017; Schuler IV and Montejo, 2019). There are also ways green spaces can be beneficial to respiratory health, by providing some protection from anthropogenic air pollution through absorption, providing physical barriers against emission sources, or by limiting the overall area available to sources of pollution such as traffic or buildings (van den Bosch and Nieuwenhuijsen, 2017).

Our results showing increased odds for asthma and allergic rhinitis confirm previous results by some authors (Andrusaityte et al., 2016; Dadvand et al., 2015; Tischer et al., 2017). However, they are also contradictory to results from others (Alcock et al., 2017; Gernes et al., 2019; Lovasi et al., 2008; Sbihi et al., 2015; Tischer et al., 2018). When considering other meta-analyses, that conducted by (Lambert et al., 2017) found too many inconsistencies between studies to accurately assess possible associations and that done by (Fuertes et al., 2016) found differential associations with NDVI within a 500 m buffer and allergic rhinitis depending on the cohort and no significant associations from meta-analyses.

These differences between the results showing positive or negative associations between allergic and respiratory symptoms and green space could be partially due to differences in cohorts or age groups, and inclusion of confounding variables. More likely, in our view, the inconsistencies in exposure definition may be driving this difference. The term “green space” itself may be part of the problem, as it can refer to multiple types of land cover, from homogenous grass fields to highly diverse forests. Taylor and Hochuli find that the term “green space” used in the literature can have up to six different meanings, largely falling into two categories describing either naturally vegetated areas or urban green space (Taylor and Hochuli, 2017). These two categories are both considered “green space”, however they may impart different impacts. Of the similar studies looking into respiratory health, most use NDVI as an indicator of green space which covers both natural vegetation and urban green space. While NDVI is a specific measure with a clear definition, the values change throughout the year depending on vegetation growth and seasonal effects. In wide area studies covering different years and seasons it is difficult to have consistent calibrated NDVI values, even if annual averages are used. In the present study, the decision to include exposures based on CLC rather than NDVI was made based on the capacity of CLC to separate between, and even within, agricultural, forest and grass areas, however this makes direct comparison between many other studies difficult.

In considering the distinction between forest types, we found significant associations between coniferous forests and respiratory health outcomes, although the number of children living in proximity to these forest types was relatively small in our study. To our knowledge, our study is the first to suggest an adverse significant relationship between living close to coniferous forests and respiratory health. It is not clear, however, if this result is due to something specific to conifers themselves, or potential differences in pollens, humidity, or mould spores (Kurlandsky et al., 2011). We note that most of our study participants were from Italy, and that no cohorts were examined from Nordic countries where coniferous forests are dominant. Sensitization to conifer pollens – especially from the cypress and pine families - among allergic patients, however, is highly prevalent also in Mediterranean areas (Domínguez-Ortega et al., 2017; Gastaminza et al., 2009; Marchetti et al., 2017) and the prevalence of sensitization to these types of pollens have been increasing in the last decades (Charpin et al., 2005).

No associations were found between grey or blue space for any of the allergic or respiratory outcomes. In terms of blue space, a conclusive statement cannot be made because of the lack statistical power. For grey spaces, our results are consistent with pooled analyses of four studies on Spanish children done by (Tischer et al., 2017), who found no statistically significant associations for grey space determined by CLC within 300 m buffers and wheezing, asthma and allergic rhinitis. Another study by (Ebisu et al., 2011) found a significant association between urban land use and wheeze severity in American infants, but the significance of this association disappeared when the models were adjusted for NO_2.

Again, here is the question regarding the definition of exposure. In the case of (Tischer et al., 2017) where CLC was also used at a buffer radius of 300 m, our results are also consistent with no association between grey space and any of the allergic and respiratory outcomes. In the case of (Ebisu et al., 2011), their exposures are estimated from the U.S. National Land Cover Database, which may differ from CLC, and they also considered a much larger buffer surrounding the residence (1540 m). Further, it may be problematic to compare urban areas in Europe to those in the United States as the urban topography and green spaces are dissimilar.

Several studies have explored the benefits of rural and agricultural exposures on the immune system and respiratory health due to the influence of the local microbiome and its impact on immunoregulation (Deckers et al., 2019; Frei et al., 2019; Hanski et al., 2012). When evaluating agricultural space, our results show a moderately protective effect for all the respiratory outcomes, although not at a statistically significant level.

Strengths and limitations:

Our analyses used CLC to define exposures to green space and other land cover features. As our cohorts span across four countries, the standardization of the exposures across Europe provided by CLC allows for pooled results and consistency across studies.
Another significant advantage of CLC is that it can distinguish green spaces between coniferous, deciduous and mixed forests, a necessary step towards understanding the health effects of specific vegetation types and untangling the complexities inherent in the interactions between respiratory health and green space. To our knowledge, our study presents the first results to assess the associations between the type of nearby forest cover and allergic and respiratory impacts. It is also, to our knowledge, the first study to use CLC to estimate residential green space in relation to health outcomes. The use of CLC, rather than NDVI to determine green space exposure, however, means we cannot directly compare our results with many other studies. CLC data does not capture small green spaces well which some have suggested renders its use inappropriate in urban areas (Annerstedt et al., 2012; Mitchell et al., 2011). Consequently, our observations may be confounded due to exposure misclassification.

Quantifying land cover is only an indirect way of assessing exposure. The chosen buffer size can also affect the results. Our choice of a 500 m buffer is supported by (Browning and Lee, 2017), and our results were consistent when changing the buffer radius to 300 m or 1000 m (Table S5 in the Online Supplement). A further concern is that CLC is only available for specific years, which may mean that for some of the younger children the exposure was measured before they were born. In most cases, however, the CLC values for most areas from 2006 to 2012, for example, do not change enough to suggest this is an issue, and we can assume CLC values are relatively constant over our time period for most areas.

This study meta-analyses heterogeneous population-based paediatric cohorts with different protocols, outcome definitions and with different age-ranges. The differences in age across cohorts could be of concern, as the relation between the clinical phenotypes and the exposure might vary by age. However, we found that the associations between type of land cover and health outcomes were homogeneous across three different age groups (3-5, 6-10, and 11-14 years; Table S3 in the Online Supplement) suggesting that CLC exposures have similar effects on respiratory symptoms within the age-range of 3-14 years. The definitions adopted for asthma, wheezing, allergic rhinitis, and eczema in all studies were validated in previous studies. The differences in the wording across the cohorts are minor and, moreover, the meta-analyses showed an overall great homogeneity across studies in the associations between land cover features and outcomes, suggesting that differences in protocols and definitions might have biased our estimates only to a minor extent.

Two considerable limitations of our study are that daily activity of participants has not been assessed and that only current residential exposure is explored. We acknowledge that moving behaviour has not been assessed, however if it was different between cases and non-cases (e.g. families of children with wheezing and rhinitis are more likely to move to greener areas), it could have affected the estimates of our study or may provoke a reverse causation. However, we observed that the effect size of the associations of green-space with respiratory and allergic symptoms was stronger when looking at the outcomes reported in the last 12 months, during which the likelihood of having moved is lower as compared to the lifetime outcomes. This suggests that there has not been a differential error according to the disease status of the children and, as a consequence, it is more likely that the lack of information on house moving history has biased our results toward the null effect by reducing the strength of our associations. Moreover, we showed that the associations were homogeneous across different age groups (Table S3 in the Online Supplement). As these age groups should be homogeneous in terms of the risk of moving (e.g. children within the group 11-14 years all have a similar probability to have moved in their lifetime, and have greater probability than children within the group 3-5 years), the homogeneity across these three groups indicates that, if moving behaviour has influenced our results, it has biased them only to a minor extent.

The number of children that were exposed to some forest types, especially coniferous and mixed forests, was relatively small, affecting the statistical power of the analyses. This is likely to increase the risk of type-2 error, e.g. not being able to find an association where there is actually one (“false-negative conclusion”), and may have prevented potentially significant associations. Moreover, as low power is affecting the size of the confidence intervals of the associations, it should be taken into account when interpreting our results, and both significant and non-significant results should be interpreted with caution.

Finally, the mechanisms of how exactly green space and biodiversity impact allergic and respiratory health remain unclear. Along with pollen, factors such as humidity, moulds and local climate conditions may also be implicated. Air pollution exposure is another concern for respiratory heath (Thurston et al., 2017). Yet, it is unlikely that air pollution biased the associations between green space and the health outcomes observed in our study, since further adjusting for residential NO_2 or PM_{10} levels did not substantially change the estimated associations. However, we cannot rule out that other air pollutants may play a role.

5. Conclusions

Data collected from nine different European paediatric cohorts was meta-analysed to investigate potential associations between current residential land cover and common respiratory and allergic childhood diseases. Our results indicate that living close to large green space areas, in particular coniferous forests, may increase the risk of developing wheezing, asthma and allergic rhinitis in children.

Our findings also support research showing that agricultural areas near children's homes may have a protective effect on respiratory health, while exposure to urban/grey space did not seem to impact the development of wheezing, asthma or rhinitis. Additional studies evaluating both the type and quality of green space and its use, as well as the interaction with air and soil pollution in relation to respiratory conditions, should be conducted in order to clarify the underlying mechanisms behind the adverse respiratory impacts associated with green space.

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Contributors:

The corresponding author Eija Parmes and Cara Nichole Maesano conceived of the study. Eija Parmes was responsible for CLC exposure estimates. Giancarlo Pesce designed the statistical analysis plan and performed the statistical analyses. Cara Nichole Maesano and Giancarlo Pesce drafted the first version of the manuscript. All the authors contributed in the collection of data in/from the original studies, discussion of the statistical analysis plan and interpretation of the results. All the authors critically reviewed and approved the final version of the manuscript. Eija Parmes had final responsibility for the submission of the publication.

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