Environmental Research 189 (2020) 109914

Contents lists available at ScienceDirect

Environmental Research

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

Residential green space and medication sales for childhood asthma: A longitudinal ecological study in Belgium

Raf Aerts[a,b,c,d,e,*], Sebastien Dujardin[c,f], Benoit Nemery[g], An Van Nieuwenhuyse[a,g,1], Jos Van Orshoven[c], Jean-Marie Aerts[h], Ben Somers[c], Marijke Hendrickx[e], Nicolas Bruffaerts[e], Mariska Bauwelinck[i], Lidia Casas[g,j], Claire Demoury[a], Michelle Plusquin[d], Tim S. Nawrot[d,g]

[a] *Risk and Health Impact Assessment, Sciensano (Belgian Institute of Health), Juliette Wytsmanstraat 14, BE-1050, Brussels, Belgium*
[b] *Division Ecology, Evolution and Biodiversity Conservation, University of Leuven (KU Leuven), Kasteelpark Arenberg 31-2435, BE-3001, Leuven, Belgium*
[c] *Division Forest, Nature and Landscape, University of Leuven (KU Leuven), Celestijnenlaan 200E-2411, BE-3001, Leuven, Belgium*
[d] *Center for Environmental Sciences, University of Hasselt, Agoralaan D, BE-3590, Diepenbeek, Hasselt, Belgium*
[e] *Mycology and Aerobiology, Sciensano (Belgian Institute of Health), Juliette Wytsmanstraat 14, BE-1050, Brussels, Belgium*
[f] *Department of Geography, Institute of Life Earth and Environment (ILEE), University of Namur, Namur, Belgium*
[g] *Center for Environment and Health, Department of Public Health and Primary Care, University of Leuven, Herestraat 49-706, BE-3000, Leuven, Belgium*
[h] *Division Animal and Human Health Engineering, University of Leuven (KU Leuven), Leuven, Belgium*
[i] *Interface Demography, Department of Sociology, Vrije Universiteit Brussel, Pleinlaan 5, BE-1050, Brussels, Belgium*
[j] *Epidemiology and Social Medicine, University of Antwerp, Universiteitsplein 1-R.232, BE-2610, Wilrijk, Antwerp, Belgium*

ARTICLE INFO

Keywords:
Pediatric asthma
Environmental epidemiology
Medication sales
Residential green space
Respiratory health

ABSTRACT

Background: Living in green environments has been associated with various health benefits, but the evidence for positive effects on respiratory health in children is ambiguous.

Objective: To investigate if residential exposure to different types of green space is associated with childhood asthma prevalence in Belgium.

Methods: Asthma prevalence was estimated from sales data of reimbursed medication for obstructive airway disease (OAD) prescribed to children between 2010 and 2014, aggregated at census tract level ($n = 1872$) by sex and age group (6–12 and 13–18 years). Generalized log-linear mixed effects models with repeated measures were used to estimate effects of relative covers of forest, grassland and garden in the census tract of the residence on OAD medication sales. Models were adjusted for air pollution (PM_{10}), housing quality and administrative region.

Results: Consistent associations between OAD medication sales and relative covers of grassland and garden were observed (unadjusted parameter estimates per IQR increase of relative cover, range across four strata: grassland, $\beta = 0.15$–0.17; garden, $\beta = 0.13$–0.17). The associations remained significant after adjusting for housing quality and chronic air pollution (adjusted parameter estimates per IQR increase of relative cover, range across four strata: grassland, $\beta = 0.10$–0.14; garden, $\beta = 0.07$–0.09). There was no association between OAD medication sales and forest cover.

Conclusions: Based on aggregated data, we found that living in close proximity to areas with high grass cover (grasslands, but also residential gardens) may negatively impact child respiratory health. Potential allergic and non-allergic mechanisms that underlie this association include elevated exposure to grass pollen and fungi and reduced exposure to environmental biodiversity. Reducing the dominance of grass in public and private green space might be beneficial to reduce the childhood asthma burden and may simultaneously improve the ecological value of urban green space.

---

[*] Corresponding author. Sciensano, Juliette Wytsmanstraat 14, BE-1050, Brussels, Belgium.
E-mail address: raf.aerts@sciensano.be (R. Aerts).
[1] Present address: Department of Health Protection, Laboratoire National de Santé (LNS), Dudelange, Luxembourg.

https://doi.org/10.1016/j.envres.2020.109914
Received 25 April 2020; Received in revised form 3 July 2020; Accepted 3 July 2020

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by airway hyper-responsiveness and reversible airflow limitation (Carr and Bleecker, 2016; Papi et al., 2018). Asthma is the most common non-communicable disease among children (Milligan et al., 2016; WHO, 2017; Papi et al., 2018) and its prevalence is increasing globally (Cates, 2001), parallel with continuing urbanization (Lundbäck et al., 2016). Respiratory disorders including chronic asthma and rhinitis may cause insomnia and daytime fatigue (Van Herck et al., 2018), reduce levels of daytime physical activity and affect school and social performance (Diette et al., 2000; Sullivan et al., 2018; Vandenplas et al., 2018; Gruffydd-Jones et al., 2019). During adolescence and adulthood, asthma may be an important, underdiagnosed underlying condition for other health problems, including depression and cardiovascular disease (Akula et al., 2018; Strand et al., 2018; Tattersall et al., 2018). Although the number of asthma-related deaths is declining (Ebmeier et al., 2017) and the increase in prevalence may be levelling off in the high-level income countries (Lundbäck et al., 2016; Patrick et al., 2020), asthma remains an important public health problem (Ehteshami-Afshar et al., 2016; Linneberg et al., 2016).

Environmental exposures to traffic-related air pollution, fungi, second-hand tobacco smoke, and aeroallergens, in combination with genetic predisposition and early life exposure to antibiotics, are major risk factors for developing and exacerbating allergic and non-allergic asthma (Flamant-Hulin et al., 2013; Dannemiller et al., 2016; Liu et al., 2016; Tétreault et al., 2016; Khreis et al., 2017; Papi et al., 2018; Guilbert et al., 2018; Eguiluz-Gracia et al., 2019; Murrison et al., 2019; Parmes et al., 2020; Buteau et al., 2020; Patrick et al., 2020). Vegetation may have the potential to mitigate some of these harmful environmental exposures and could therefore protect against asthma and other respiratory conditions (Tischer et al., 2017; Squillacioti et al., 2019; Fuertes et al., 2020). For instance, urban green spaces may mitigate outdoor air pollution and hereby prevent asthma exacerbations (Markevych et al., 2017). Urban green spaces may also facilitate asthma control by reducing stress or improving physical activity (DePriest et al., 2019). Furthermore, according to the biodiversity hypothesis, biodiversity in green spaces may support the immune system through beneficial effects on the composition and diversity of the human microbiome, and hereby protect against the development of chronic inflammatory diseases, including asthma (Hanski et al., 2012; Haahtela et al., 2013).

However, green spaces may also produce and emit allergenic pollen (Cariñanos et al., 2017; Kasprzyk et al., 2019; Lara et al., 2019). An increasing number of studies has found that allergenic pollen, in combination with air pollution and other agents such as fungal spores, endotoxins and mycotoxins, may initiate airway inflammation and trigger allergic and non-allergic asthma, asthma medication sales and hospital admissions for asthma (Dadvand et al., 2014; Erbas et al. 2013, 2018; Guilbert et al., 2018; Lambert et al. 2017, 2019; Idrose et al., 2020). Housing quality and other dimensions of socioeconomic status may also affect respiratory health and are, like air pollution, potential confounders of the association between green space, asthma prevalence and asthma medication sales (Donaldson et al., 2000; Casas et al., 2016; Hughes et al., 2017; Orellano et al., 2017; Sahni et al., 2017).

The health benefits of exposure to green space are increasingly recognized (James et al., 2015; van den Bosch and Sang, 2017; Twohig-Bennett and Jones, 2018), but the epidemiological evidence for beneficial effects of green space on asthma prevalence and severity remains heterogeneous and inconclusive (Dadvand et al., 2019; Ferrante et al., 2020; Sullivan and Thakur, 2020). In a systematic review of 11 studies and meta-analysis of three studies investigating the association between residential greenness and asthma, Lambert et al. (2017) found no significant overall association between asthma and a residential greenness index derived from remote sensing data (Normalized Difference Vegetation Index [NDVI] in a 100 m buffer; $n = 3$ studies, pooled OR: 1.01, 95% CI: 0.93–1.09). In a follow-up systematic review of studies in children, Hartley et al. (2020) reported that only one out of seven articles published since 2017 found evidence for a protective effect of greenness on asthma (Donovan et al., 2018; variation in greenness and diversity of native land cover types were both associated with lower risks for childhood asthma). The six other studies found no direct association between greenness and asthma.

Research on the association between residential green space and asthma has tended to focus on greenness rather than on green space types. The main disadvantage of greenness, estimated by NDVI, is that it is only a coarse indicator of green space quality (Rugel et al., 2017; Gernes et al., 2019). NDVI fails to address differences in vegetation composition and structure and therefore inadequately captures potentially different impacts on human health (Alcock et al., 2017; Wood et al., 2018; DePriest et al., 2019). A better understanding of the relationships between asthma prevalence and exposure to different types of green space may help to elucidate the mechanisms that underlie these associations (Parmes et al., 2020), guide urban planning decisions (Alcock et al., 2017), and help asthma patients to avoid environmental triggers, reducing the burden of asthma (Halken, 2004; D'Amato et al., 2020). The present study aimed to address this issue by examining medication sales for childhood asthma in residential areas in Belgium and associations with relative covers of three different green space types, i.e. forest, grassland and residential gardens. We hypothesized that medications sales for childhood asthma would be associated with residential green space types, with and without adjustment for potential confounding variables, and that the direction and magnitude of the association would vary among green space types (Fig. 1).

2. Methods

2.1. Study design

This study is part of the GRESP-HEALTH project (Casas et al., 2015), which is a nationwide ecological study on the association between residential exposure to green spaces and specific morbidity in Belgium. Belgium (11.43 million inhabitants in 2019; 30,528 km^2) has three administrative regions: the Walloon Region (Wallonia, 16,844 km^2), the Flemish Region (Flanders, 13,522 km^2), and the Brussels Capital Region (161 km^2). Data were available and analyzed at census tract level. The census tracts are the official administrative spatial units for statistical purposes at higher resolution than the municipality ("statistical sectors"), defined by the Belgian Statistical Office (Statbel). The total number of census tracts in Belgium is 19782, with an average census tract surface area of 1.54 km^2 (median 0.46 km^2; range 0.01–63 km^2) and an average of 539 inhabitants (median 1475; range 0–7029) (Vademecum Statistische Sectoren, 2019).

2.2. Study population

This study used health care data from the Belgian social security agency InterMutualistisch Agentschap-L'Agence InterMutualiste (IMA-AIM). The IMA-AIM manages health care data collected by the seven Belgian health insurance funds. In Belgium, health insurance is mandatory and the population in the IMA-AIM database corresponds to about 98% of the Belgian population (as registered in the national register). The IMA-AIM provided data on reimbursed medication sales for obstructive airway disease (OAD) from 2010 to 2014. The data included the number of individuals aged 6–18 years old per census tract and per year for whom at least one refundable medication was prescribed at least once during the study period (2010–2014) as well as the number of registered individuals aged 6–18 years old per census tract (Fig. 2). OAD medication was defined as all reimbursed drugs included in the ATC (Anatomical Therapeutic Chemical) code R03 (medication for OAD: adrenergic inhalants, adrenergics for systemic use and other inhalants and systemic drugs for OAD). These drugs include short-acting and long-acting β-agonists (bronchodilators) as well as inhaled corticosteroids

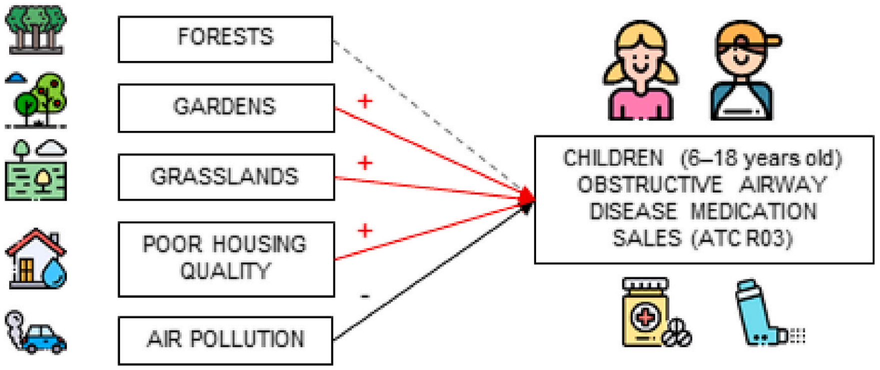

Fig. 1. Conceptual diagram of the effects of green space variables and potential confounders on medication sales for childhood asthma in Belgium. Red arrows and a + sign indicate positive associations in our final models, whereas black arrows and a – sign indicate inverse associations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

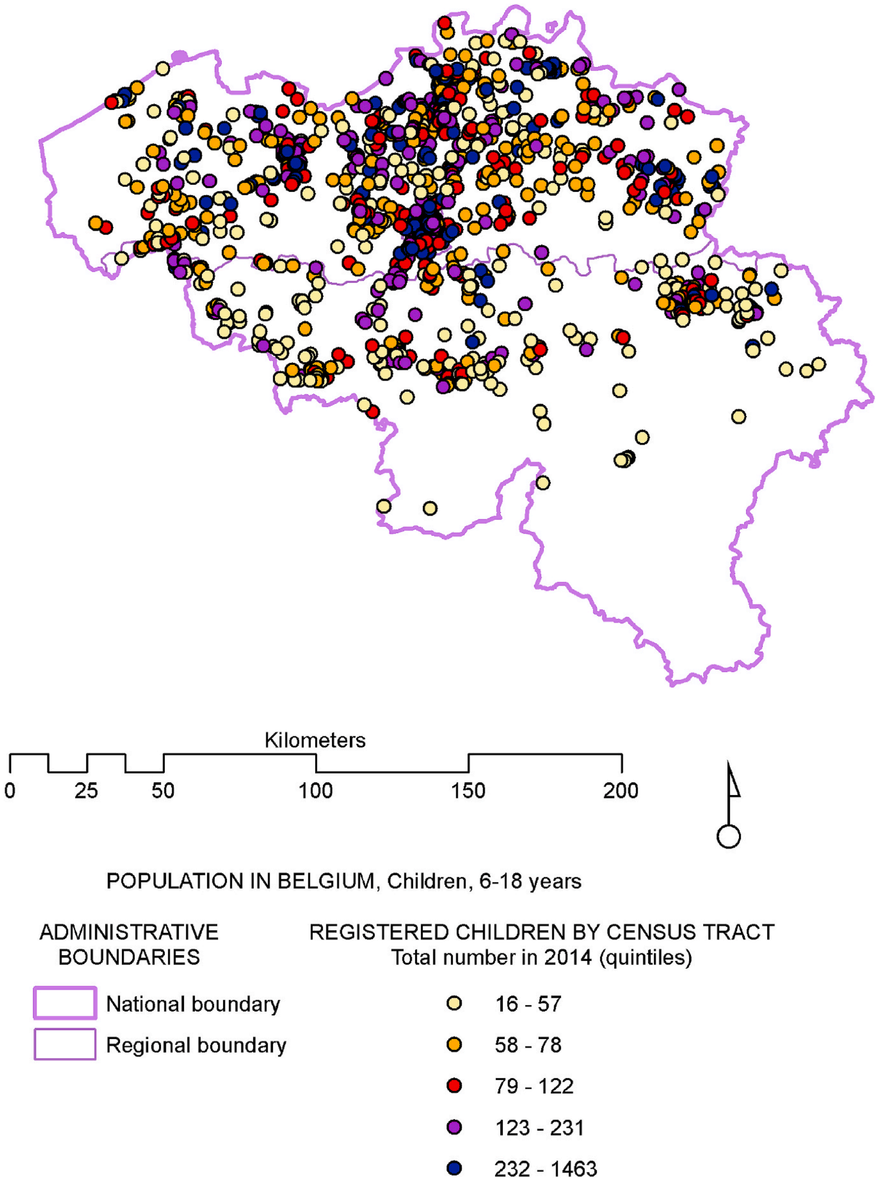

Fig. 2. Distribution and size of the study population (children aged 6–18 years) in Belgium. Census tracts with no more than 5 reimbursed persons in at least one year during the study period (2010–2014) were excluded due to privacy reasons. Data shown is for the year 2014.

(ICS) to treat asthma in children (Guilbert et al., 2014). The sales of these drugs to treat chronic obstructive pulmonary disease (COPD) in adults are not within the scope of this study. The aggregated data did not contain information on the frequency of use. Census tracts with no more than 5 reimbursed persons in at least one year during the study period were excluded by IMA-AIM due to privacy reasons. All health data were used under license of IMA-AIM and the protocol for this study did not require ethics approval or consent to participate.

2.3. *Asthma medication sales*

The 12-month prevalence (period prevalence PP, %) of respiratory medication sales was used as the health outcome variable, as a proxy for the prevalence of asthma in the 6–18 years old age group. The PP was calculated as the percentage of reimbursed patients relative to the number of registered persons within the considered age segment per census tract per year. The PP was calculated for sex and age groups separately, resulting in four strata: girls, 6–12 years old (number of census tracts included in the study $n_{CT} = 412$), girls, 13–18 years old ($n_{CT} = 110$), boys, 6–12 years old ($n_{CT} = 1144$) and boys, 13–18 years old ($n_{CT} = 206$).

2.4. *Exposure to residential green space*

Land cover data were provided by the Belgian National Geographic Institute (NGI-IGN). Green space types and their relative cover were extracted from the Top10Vector database ("Soil cover and vegetation" dataset, version 1.1 2011). Top10Vector is the NGI's database of topographic vector data layers and geometrically the most accurate data available for the entire Belgian territory (data have been collected during field campaigns of the topo-geographic inventory of Belgium and were transcribed on aerial photographs at the scale of 1:10,000). First, vector data (polygons) were extracted from the land cover data set of Top10Vector for eight land cover types associated with vegetation: 1. coniferous woodland, 2. predominantly coniferous mixed woodland, 3. mixed woodland, 4. predominantly broad-leaved mixed woodland, 5. broadleaved woodland, 6. permanent grassland or hay meadow (permanent grassy land, grazed or intended for hay production), 7. lawn (periodically mown grassy land, found for example on sports fields, on hard shoulders and road embankments and in parks) and 8. garden (ornamental gardens or vegetable gardens near residences) (Fig. S1). Using a spatial overlay procedure between the land cover data and census tract boundaries, the cumulative cover (m^2) of each of these eight land cover types within every census tract in Belgium was determined. Forest cover (m^2) was calculated as the sum of the five woodland covers (land cover types 1–5) and grassland cover (m^2) as the sum of grasslands, meadows and lawns (land cover types 6 and 7). Forest cover, grassland cover and garden cover at the census tract level were expressed as relative cover (%). Spatial overlays were performed using the package 'sf' (Simple Features for R, version 0.8–0) implemented in the R system for statistical computing. The main geometric operations were performed using the functions 'st_intersection' for identifying features polygons overlaying with census tracts and 'st_area' for measuring the surface area (in m^2) of each land use category per census tract. The total surface area per census tract was then calculated using the function 'summarize' from the 'dplyr' (version 0.8.3). The landscape in the Walloon Region in the south is relatively sparsely populated and characterized by relatively large expanses of coniferous and mixed woodland (Fig. S1). The Flemish Region in the north is highly urbanized with relatively few woodlands and a high proportion of permanent grassland (Fig. S1).

2.5. *Potential confounders*

The annual mean concentration of particulate matter <10 μm (PM_{10}; Fig. S2) and housing quality (Fig. S3) were included in our analyses as adjustment variables. Air pollution data were provided by the Belgian Interregional Environment Agency (IRCEL-CELINE). The data at census tract level were generalized from a high resolution model (25 m × 25 m) of the annual mean PM_{10} concentrations (μg/m^3) for the year 2015. The air pollution model was based on a spatial interpolation of air pollution measurements using data from monitoring stations and CORINE Land Cover (CLC) information along with a dispersion model (Janssen et al., 2008; Lefebvre and Vranckx, 2013). Housing quality data were derived from the 2001 census and were provided by the Belgian Statistical Office. The proportion of houses with insufficient or basic housing quality at the census tract level was calculated as the sum of the proportions of houses with 'insufficient' and with 'basic' housing quality (i.e. the two lowest housing quality scores on a scale with five classes). Air pollution in Belgium generally decreases from north to south with major hotspots in Ghent, Antwerp and the Brussels Capital Region (Fig. S2). The proportion of houses with basic or insufficient quality decreases from west to east, but remains relatively high along the former industrial backbone in the Sambre and Meuse valley in the Walloon Region, where other indicators for low SES such as unemployment are also high (Aerts et al., 2020) (Fig. S3).

2.6. *Statistical analyses*

Non-parametric Kruskal-Wallis analysis of variance was used to test for differences in the average 12-month prevalence of OAD medication sales among age and sex strata. For the main analysis, generalized mixed effects models with repeated measures based on the Poisson distribution with log-link function were used to estimate the effects of green space type and relative cover on OAD medication sales (12-month prevalence at census tract level) for sex and age groups separately. Because models based on the Poisson distribution require non-negative integer values (count data) for the dependent variable, the 12-month prevalence was rounded to the nearest whole number. Unadjusted and confounder-adjusted models were evaluated. In the unadjusted models, relative covers of forest, grassland and garden were defined as fixed effects (all entered in the same model). Year (2010–2014) was used as the time variable. In the adjusted models mean annual PM_{10} concentration and proportion of houses with basic or insufficient quality were added to the fixed effects and a random effect block of administrative region (intercept only) was added to account for potential autocorrelation between census tracts within the same region. Models were run with compound symmetry (equal variance) covariance structures. Because models based on the Poisson distribution may be susceptible to overdispersion (variance in the observed data may be higher than expected), we used the robust estimation method to calculate the covariance matrix of parameter estimates. To obtain parameter estimates that reflect changes in OAD medication sales per interquartile range (IQR) increase of the fixed effect variables, the variables of the fixed effects were divided by their stratum-specific IQR (Table 1) prior to their inclusion in the models. In addition, we ran models without repeated measure, using the 5-year average medication sales data per stratum as the outcome variable. Finally we also ran fully adjusted models that included a random effect of administrative region (in addition to the random intercept). Statistical analyses were performed with IBM SPSS Statistics Subscription 11–2018 software.

3. Results

3.1. *Census tract characteristics*

The characteristics of the census tracts that were included in the study are presented in Table 1 (means and SD, medians and IQR). The proportions of green space types within the census tract varied only slightly among strata: the average proportion of gardens ranged between 38.1 and 39.2%; the average proportion of grassland between 6.4 and 10.1%; and the average proportion of forest between 2.2 and 3.1%. The

Table 1

Characteristics of the census tracts included in the study.

	Girls		Boys	
	6–12 years old	13–18 years old	6–12 years old	13–18 years old
N (tracts)	412	110	1144	206
PM_{10} ($\mu g/m^3$)	19.5 (2.4)	19.9 (2.3)	19.1 (2.4)	19.6 (2.7)
	19.5 [3.3]	20.2 [2.9]	18.9 [3.2]	19.6 [3.4]
Insufficient or basic housing quality (%)	39.4 (13.4)	39.3 (14.2)	37.5 (13.5)	38.4 (13.5)
	39.3 [20.7]	38.1 [22.7]	37.1 [21.2]	38.7 [21.3]
Relative cover				
Gardens (%)	38.1 (15.4)	38.2 (16.6)	39.2 (14.8)	38.6 (15.4)
	40.9 [22.1]	41.9 [24.6]	41.5 [19.3]	40.9 [23.1]
Grassland (%)	8.2 (8.2)	6.4 (6.5)	10.1 (10.4)	8.6 (8.8)
	6.0 [9.9]	4.7 [8.7]	7.1 [11.9]	6.5 [11.1]
Forest (%)	2.7 (4.8)	2.2 (3.7)	3.1 (5.4)	2.6 (4.7)
	0.79 [3.1]	0.42 [2.8]	1.04 [3.7]	0.78 [3.1]

Data are means with (standard deviations) and medians with [interquartile range IQR]. PM_{10} data is the annual mean for the year 2015; housing quality data is derived from the 2001 census; land cover data is derived from the 2011 NGI topographical map.

average annual PM_{10} concentration (2015) over all census tracts included in the study was 19–20 μg/m^3 (the WHO guideline value for the mean annual concentration of PM_{10} is 20 μg/m^3) and the average proportion of houses with insufficient or basic housing quality varied between 37.5 and 39.4%. Also these variables varied very little between sex and age strata (Table 1).

3.2. *Asthma medication sales*

The average 12-month prevalence (PP) of OAD medication sales across sex and age groups between 2010 and 2014 was 12.2% (SD: 5.2). Within strata the average period prevalence varied little between years (Fig. 3) (spatial variation within the strata is shown for the year 2014 in Figures S4–S7). The average 12-month prevalence differed significantly between sex and age groups (Kruskal Wallis $\chi^2 = 500.3$, df = 3, Bonferroni adjusted $p < 0.001$). The 12-month prevalence of OAD medication sales was the highest in the 6–12 year old age groups: boys [PP(SD): 13.5% (4.0)] vs. girls [PP(SD): 10.2% (3.2)]. The prevalence was lower in the 13–18 year old age group: boys [PP (SD): 8.9% (2.5)] vs. girls [PP (SD): 8.1% (2.3)].

3.3. *Associations with green space*

3.3.1. *Unadjusted associations*

In unadjusted models with only fixed effects of land cover, significant associations between OAD medication sales and grassland and garden cover were observed (Fig. 4; Table S1). The unadjusted parameter estimates varied little among sex and age groups and ranged between 0.15 and 0.17 (per IQR increase of relative grassland cover) and between 0.13 and 0.17 (per IQR increase of relative garden cover) (Table S1). There were no significant associations between OAD medication sales and forest cover in the unadjusted models (Fig. 4; Table S1).

3.3.2. *Adjusted associations*

The associations between OAD medication sales and relative covers of grassland and gardens remained significant after adjusting for air pollution and housing quality (Fig. 4; Table S1). The parameter estimates for grassland cover were larger in the 13–18 year old age group (girls, $\beta = 0.137$, 95% CI: 0.053–0.221; boys, $\beta = 0.117$, 95% CI: 0.095–0.140) than at younger age (girls, $\beta = 0.107$, 95% CI: 0.072–0.142; boys, $\beta = 0.099$, 95% CI: 0.063–0.135) (all $p < 0.001$) (Fig. 4; Table S1). We observed consistent direct associations between OAD medication sales and relative cover of gardens (6–12 year old girls, $\beta = 0.088$, 95% CI: 0.069–0.107; 6–12 year old boys, $\beta = 0.071$, 95% CI: 0.048–0.094; 13–18 year old boys, $\beta = 0.090$, 95% CI: 0.071–0.109) (all $p < 0.001$). The uncertainty of this association was larger in 13–18 year old girls where the sample size was limited ($\beta = 0.086$, 95% CI: −0.030–0.201, $p = 0.147$) (Fig. 4; Table S1). There was a small inverse (protective) association between OAD medication sales and relative cover of forest in 13–18 year old girls ($\beta = -0.013$, 95% CI: −0.025–0.000, $p = 0.048$). In the other strata, no association between OAD medication sales and relative cover of forest was observed (Fig. 4; Table S1).

Across all strata, we observed consistent inverse associations

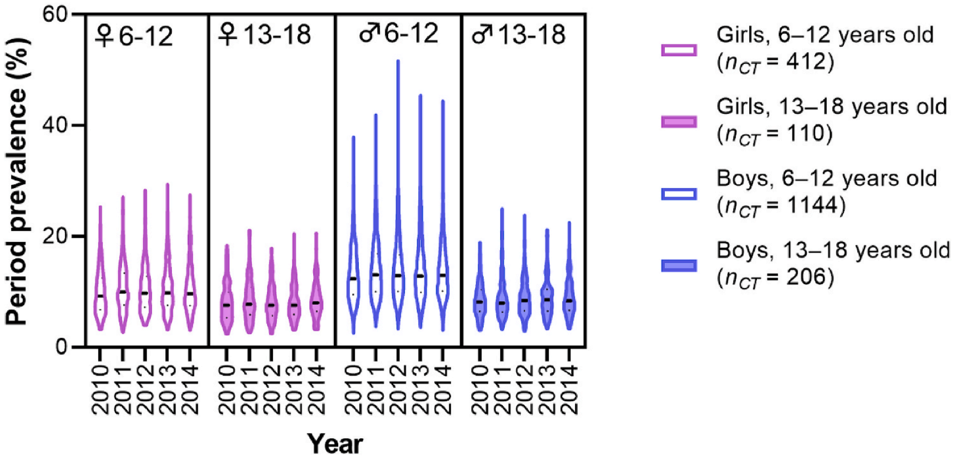

Fig. 3. Asthma medication sales for children aged 6–18 years in Belgium for the years 2010–2014 [period prevalence of medication sales for obstructive airway diseases (ATC R03) at the level of census tracts (CT)].

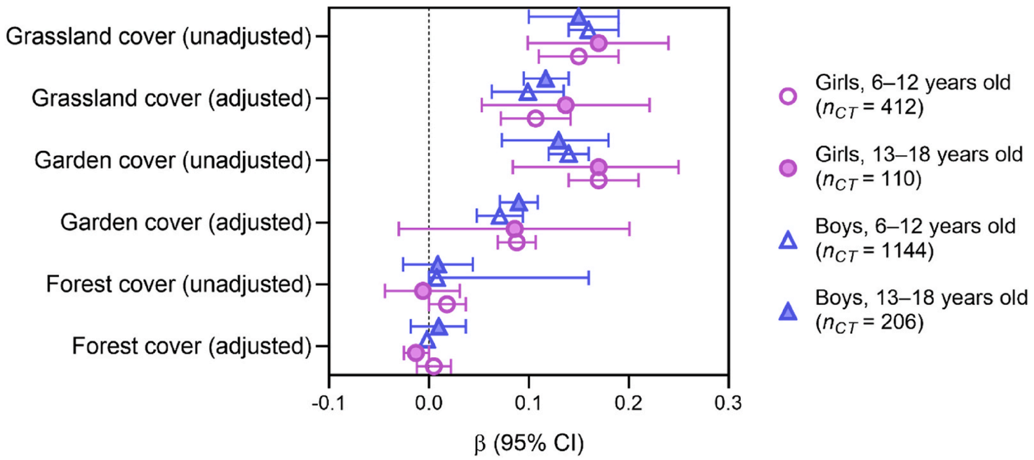

Fig. 4. Unadjusted and adjusted associations between residential green space and asthma medication sales in children aged 6–18 years in Belgium [12-month prevalence of medication sales for obstructive airway disease (ATC R03) at the level of census tracts (*CT*)]. Parameter estimates β (per stratum-specific IQR increase, see Table 1) and 95% confidence intervals are from generalized log-linear mixed-effects models with repeated measures (2010–2014). Adjusted estimates are derived from models that were adjusted for housing quality and air pollution (PM_{10}) and that included a random effect of administrative region. Grassland cover includes permanent grassland, hay meadows and lawns; garden cover includes ornamental gardens and vegetable gardens near residences; forest cover includes coniferous, mixed and broadleaved woodlands. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

between obstructive airway disease medication sales and annual mean PM_{10} concentrations (parameter estimates β between −0.113 and −0.093, all $p < 0.001$) (Fig. S8). We also observed direct associations between OAD medication sales and basic or insufficient housing quality but not in 13–18 year old girls (6–12 year old girls, β = 0.061, 95% CI: 0.043–0.079; 6–12 year old boys, β = 0.049, 95% CI: 0.024–0.074; 13–18 year old boys, β = 0.112, 95% CI: 0.050–0.175) (all $p < 0.001$) (Fig. S8; Table S1). The fully adjusted model did not improve when a random effect for administrative region was entered (compared to a model with only a random intercept).

3.3.3. Associations without repeated measures

The parameter estimates from the adjusted models based on the 5-year average period prevalence did not vary much from those of the fully-adjusted repeated measures models and supported the associations between grassland and garden cover and OAD medication sales (Table S2).

4. Discussion

4.1. Main findings

We investigated childhood asthma medication sales in Belgium by assessing associations between aggregated data of reimbursed medication sales for OAD and data on residential exposure to grassland, gardens and forest, adjusting for potential effects of air pollution and housing quality. Results suggest that living close to areas with high grass cover – permanent grassland, hay meadows, lawns and residential gardens – may adversely impact child respiratory health.

4.2. Comparison with other studies

The prevalence of childhood asthma is usually higher in boys than in girls but this pattern has been documented to reverse with the onset of puberty and in adulthood (Papi et al., 2018). In our sample, the 12-month prevalence of OAD medication sales was indeed higher in boys and in particular in the younger age group (6–12 year old boys; Fig. 3).

Earlier studies with different green space metrics found mixed evidence for the effects of green space on childhood asthma. A birth cohort study in New York City, USA, reported a lower prevalence of asthma (RR 0.71, 95% CI: 0.64–0.79) per standard deviation increase of street tree density (Lovasi et al., 2008). Sbihi et al. (2015) also found lower pre-school asthma incidence (OR: 0.96, 95% CI 0.93–0.99) per interquartile increase of NDVI in 100 m around the residential postal code during the perinatal period in a population-based birth cohort in British Columbia, Canada. However, a similar protective association was not found in school-aged children. A large study of surrounding greenness in relation to current asthma encompassing 3178 school children in Spain (Dadvand et al., 2014) found no significant associations between greenness and asthma in school-aged children. Conversely, a study in a New York City birth cohort reported an increased relative risk for current asthma at age 7 years (RR: 1.17, 95% CI: 1.02–1.33), but not at age 5 years, per standard deviation increase of tree canopy cover within 250 m of the address at time of birth (Lovasi et al., 2013). A study that analyzed data from nine European cohorts (including 6941 children in Italy, 877 in France, 167 in Slovenia and 78 in Poland) reported that a 10% increase in green space cover (calculated as the proportion of non-agricultural green CLC classes within 500 m of the residence) was associated with a ~10% increase in the odds of current (past 12 months) and lifetime asthma (Parmes et al., 2020). Both studies suggested that exposure to trees (or tree pollen) may increase the odds for developing asthma. A study that analyzed data from a birth cohort of children with a family history of allergic diseases found that exposure to grass pollen at birth was associated with decreased childhood lung function (Lambert et al., 2019). Andrusaityte et al. (2016) found an increase in the odds of clinically diagnosed asthma (OR: 1.43, 95% CI: 1.10–1.85) with interquartile range increase in NDVI within 100 m of the residence in preschool children in Lithuania. A similar study in preschool children in Belgium also found an association between the prevalence of asthma medication sales and the relative cover of green space derived from CLC data (Trabelsi et al., 2019).

The observed association between the proportion of houses with basic or insufficient quality and medication sales for childhood asthma supports previous findings in the literature on the effects of socio-economic status on respiratory health (O'Lenick et al., 2017; Sahni et al., 2017). Poor housing quality may be associated with inadequate ventilation, inappropriate moisture balance (dampness) and poor indoor air quality. These conditions may affect respiratory health (Francisco et al., 2017; Wang et al., 2019; Cai et al., 2020), because they may affect, among others, the levels of aeroallergens emitted by house dust mites and molds. The inverse association between air pollution (PM_{10}) and medication sales for childhood asthma differs from earlier studies that link childhood asthma to air pollution (Donaldson et al., 2000; Orellano et al., 2017; Buteau et al., 2020; Pierangeli et al., 2020), but is in line with earlier findings on medication sales in Belgium (Aerts et al., 2020). The observed inverse association may be the result of ecological bias or confounding by an unmeasured variable, such as medical practice, resulting in lower medication sales for childhood asthma in areas with a higher burden of air pollution. Such confounding has been documented before in Belgium, where strong cultural contrasts exist between the different regions (Trabelsi et al., 2019).

4.3. Potential mechanisms

Our results provide epidemiologic support for a number of potential allergic and non-allergic mechanisms that link environmental exposure to high grassland and garden cover to the development and exacerbation of asthma in children.

First, grasses and molds present in grasslands may trigger asthma in children through allergic and non-allergic pathways. Grassland ecosystems in Europe have become highly productive, species-poor and dominated by a few, highly competitive plant species as a result of intensive land use, agricultural (artificial) fertilizer application and atmospheric deposition of nutrients, in particular nitrogen (Kleijn et al., 2009; Bobbink et al., 2010; Damgaard et al., 2011; Ceulemans et al., 2014; Payne et al., 2017). Productive grasslands near residential areas may considerably increase exposure to airborne grass pollen, and this, combined with high sensitization rates to Poaceae pollen, is likely to strengthen the position of grass pollen as the leading aeroallergen worldwide (García-Mozo, 2017; Erbas et al., 2018). Environmental changes, including rising ozone and ambient CO_2 concentrations, have been documented to alter allergenic properties of pollen grains and may further increase the potency of grass pollen (Ziska et al., 2003; D'Amato et al., 2007; Beck et al., 2013; Buters et al., 2015). High exposure to grass pollen in early life has been associated with decreased lung function in children (Lambert et al., 2019). Furthermore, co-exposure to molds and fungal spores associated to organic matter in grasslands may also affect lung function and induce airway inflammation in sensitized and non-sensitized persons (Dales et al., 2000; Tham et al., 2019; Eguiluz-Gracia et al., 2020; Idrose et al., 2020). Evidence from indoor and outdoor exposure to molds suggests that non-allergic mechanisms may contribute to the association between molds and asthma in children and adolescents (Flamant-Hulin et al., 2013; Tham et al., 2017). Therefore, children that live in close proximity to areas with high grassland cover are likely to be exposed to potent mixtures of grass pollen and spores over long time periods, escalating the burden of respiratory diseases including asthma. Because residential exposure to grass pollen allergens may be difficult to avoid in areas with high grassland cover, asthma management in some patients may require drugs or immunological interventions (D'Amato et al., 2020), resulting in higher asthma medication sales.

Second, living in species-poor landscapes may be associated with chronic low exposure to environmental biodiversity, reduced skin and gut microbial diversity and chronic inflammatory diseases including asthma. Species-poor land cover types include built-up areas and the productive grassland ecosystems discussed above, but also private domestic gardens which in our study area often consist, at least partially, of fertilized, manicured lawns, according to a study of 1138 gardens in northern Belgium (Dewaelheyns et al., 2013). It is hypothesized that reduced exposure to environmental biodiversity negatively impacts the immune system by degrading the human microbiome, leading to microbial dysbiosis and increased prevalence of allergies, asthma and other chronic inflammatory diseases (Hanski et al., 2012; Haahtela et al., 2013; Rook, 2013; Ruokolainen et al., 2016; Lunjani et al., 2018; Parajuli et al., 2020). Such associations between environmental exposures, the microbiome and the development of asthma and allergic diseases are expected to be particularly important at the population level (Sbihi et al., 2019). The results of our ecological study indirectly corroborate previous studies that demonstrate the multiple benefits of individual childhood exposure to high environmental biodiversity in green spaces such as green school yards, playgrounds, ecologically managed private gardens and nearby nature (Tillmann et al., 2018; Mnich et al., 2019; Raney et al., 2019).

Third, residential exposure to grasslands and domestic gardens could increase the risk of developing or exacerbating asthma indirectly through increased exposure to other agents, including emissions associated with livestock farming (Pavilonis et al., 2013; Borlee et al., 2017; de Rooij et al., 2019), or pesticides and fertilizers used for grassland and garden management (Hernández et al., 2011; Baldi et al., 2014; Dadvand et al., 2019; Kim et al., 2020; Meftaul et al., 2020).

Finally, high residential garden cover may be associated with other characteristics of the neighborhood physical environment that could have an impact on respiratory health and asthma medication sales. Such variables include urban properties (in northern Belgium, garden cover is higher in peri-urban areas, areas with ribbon development and along built-up road segments than in rural areas; Dewaelheyns et al., 2014), which may be associated with harmful traffic-related emissions (Son et al., 2015; Alotaibi et al., 2019), and physical and socioeconomic background variables (O'Lenick et al., 2017; Bell et al., 2020; Pierangeli et al., 2020).

4.4. Strengths and limitations

A major strength of this study is that we have considered effects of specific land cover types (forest, grassland and gardens) for sex and age groups separately while adjusting for chronic air pollution and housing quality. Our measures of forest, grassland and garden cover were derived from very accurate (survey-based) land cover data and delivered more accurate measures of residential exposure to green space than exposures based on NDVI or CLC, which have been frequently used in previous research. Our results offer compelling evidence for ecosystem disservices provided by grasslands (and gardens) which have not been dealt with in depth in previous research.

However, we are aware that our research may have a number of limitations: 1. The ecological study design is prone to exposure misclassification. Health effects of green space observed at individual level may not be observed at aggregated level (census tract level). Also, individual socio-economic status differences, such as lifestyle, affluence, or general practitioner's prescription patterns, may impact associations between green space and medication sales (Trabelsi et al., 2019; Aerts et al., 2020) and these effects are masked in aggregated data; 2. The OAD medication sales period prevalence may differ from the actual prevalence of childhood asthma, because it is unlikely that all asthma patients are diagnosed and recorded in the IMA-AIM database. Some asthmatic patients may not visit doctors, some asthma cases may remain undiagnosed due to its heterogeneity in clinical presentation (Papi et al., 2018), and not all diagnosed patients may buy prescribed medication; 3. Residential exposure to green space in children may differ considerably from true exposure because it ignores dynamic time-activity patterns that include home time, school hours, recreation, and time in traffic; 4. There is a timing mismatch between the exposure data (housing quality: 2001; air pollution: 2015; land cover: 2011) and the medication sales data (2010–2014). At the time of analysis, this was the best possible match based on the availability of nationwide datasets; 5. The privacy restrictions of the study (only census tracts with >5 reimbursed prescriptions per year were included in the analysis) may have weakened the statistical power of the study; and 6. The frequency and the timing of medication use are not taken into account. Acute peaks of aeroallergen or air pollutant concentrations may temporary increase asthma hospitalization rates and asthma medication sales and use. Cohort data sets would be needed to determine exactly how such temporal environmental variations have an impact on human respiratory health (Guilbert et al., 2018).

5. Conclusions

Based on aggregated data, the evidence from this study suggests that living in close proximity to areas with high grass cover (productive grasslands and residential gardens) may negatively impact child respiratory health, indicated by prescribed asthma medication sales. Potential allergic and non-allergic mechanisms that underlie this association include elevated exposure to grass pollen and fungi and reduced exposure to environmental biodiversity. Reducing the dominance of grass in public and private green spaces by increasing non-allergenic woody vegetation cover, or by converting productive grasslands with low diversity into species-rich grasslands with wild flowers, might be beneficial strategies to reduce the childhood asthma burden and may simultaneously improve the ecological value of urban green space.

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.

The authors acknowledge the Intermutualistisch Agentschap – Agence Inter-Mutualiste (IMA-AIM) for providing the health data, Charlotte Vanpoucke (IRCEL-CELINE) and Wouter Lefebvre (VITO) for providing air pollution data and Esmeé Bijnens (U Hasselt) for aggregating air pollution data. The icons in the graphical abstract and Fig. 1 were made by Freepik from www.flaticon.com and are used under a Flaticon Basic License (with attribution).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109914.

Data Statement

The research data is confidential. The land cover data that were used to quantify residential green space (Top10Vector, identifier BE.NGI-IGN/5F4130E6-DF5C-41E6-A956-BB9F04088D11) are copyrighted (©Institut Géographique National) and were used under federal use license 2016_F014 granted by the Institut Géographique National (NGI-IGN) to the Belgian Science Policy Office (BELSPO).

Funding sources

This research has received funding from the Belgian Science Policy Office (BELSPO) through the Belgian Research Action through Interdisciplinary Networks (BRAIN-be) projects RespirIT and GRESP-HEALTH under grant agreement numbers BR/154/A1/RespirIT and BR/143/A3/GRESP-HEALTH. This research has received additional funding from the Mycology and Aerobiology service of Sciensano. LC and MB are recipients of a postdoctoral and doctoral fellowship (grant numbers 12I1517N and 11A9718N) of the Research Foundation Flanders (FWO).

Human subjects

All health data were anonymized by aggregation to census tract level and were used under license of IMA-AIM. The protocol for this study did not require ethics approval.

Credit author statement

Raf Aerts: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review and Editing, Vizualization. **Sebastien Dujardin**: Data curation, Writing – Review and Editing. **Benoit Nemery**: Conceptualization, Methodology, Writing – Review and Editing, Funding Acquisition. **An Van Nieuwenhuyse**: Conceptualization, Methodology, Writing – Review and Editing, Funding Acquisition. **Jos Van Orshoven**: Writing – Review and Editing, Funding Acquisition. **Jean-Marie Aerts**: Writing – Review and Editing, Funding Acquisition. **Ben Somers**: Writing – Review and Editing, Project Administration, Funding Acquisition. **Marijke Hendrickx**: Writing – Review and Editing, Funding Acquisition. **Nicolas Bruffaerts**: Investigation, Writing – Review and Editing. **Mariska Bauwelinck**: Methodology, Investigation, Data Curation, Writing – Review and Editing. **Lidia Casas**: Conceptualization, Methodology, Investigation, Data Curation, Writing – Review and Editing, Project Administration, Funding Acquisition. **Claire Demoury**: Writing – Review and Editing, Supervision. **Michelle Plusquin**: Writing – Review and Editing, Supervision. **Tim S. Nawrot**: Conceptualization, Methodology, Writing – Review and Editing, Supervision, Funding Acquisition.

References

Aerts, R., Nemery, B., Bauwelinck, M., Trabelsi, S., Deboosere, P., Van Nieuwenhuyse, A., Nawrot, T.S., Casas, L., 2020. Residential green space, air pollution, socioeconomic deprivation and cardiovascular medication sales in Belgium: a nationwide ecological study. Sci. Total Environ. 712, 136426. https://doi.org/10.1016/j.scitotenv.2019.136426.

Akula, M., Kulikova, A., Khan, D.A., Brown, E.S., 2018. The relationship between asthma and depression in a community-based sample. J. Asthma 55, 1271–1277. https://doi.org/10.1080/02770903.2017.1418885.

Alcock, I., White, M., Cherrie, M., Wheeler, B., Taylor, J., McInnes, R., Kampe, E.O.I., Vardoulakis, S., Sarran, C., Soyiri, I., Fleming, L., 2017. Land cover and air pollution are associated with asthma hospitalisations: a cross-sectional study. Environ. Int. 109, 29–41. https://doi.org/10.1016/j.envint.2017.08.009.

Alotaibi, R., Bechle, M., Marshall, J.D., Ramani, T., Zietsman, J., Nieuwenhuijsen, M.J., Khreis, H., 2019. Traffic related air pollution and the burden of childhood asthma in the contiguous United States in 2000 and 2010. Environ. Int. 127, 858–867. https://doi.org/10.1016/j.envint.2019.03.041.

Andrusaityte, S., Gražulevičienė, R., Kudzyte, J., Bernotiene, A., Dedele, A., Nieuwenhuijsen, M.J., 2016. Associations between neighbourhood greenness and asthma in preschool children in Kaunas, Lithuania: a case-control study. BMJ Open 6, e010341. https://doi.org/10.1136/bmjopen-2015-010341.

Baldi, I., Robert, C., Piantoni, F., Tual, S., Bouvier, G., Lebailly, P., Raherison, C., 2014. Agricultural exposure and asthma risk in the AGRICAN French Cohort. Int. J. Hyg Environ. Health 217, 435–442. https://doi.org/10.1016/j.ijheh.2013.08.006.

Beck, I., Jochner, S., Gilles, S., McIntyre, M., Buters, J.T.M., Schmidt-Weber, C., Behrendt, H., Ring, J., Menzel, A., Traidl-Hoffmann, C., 2013. High environmental ozone levels lead to enhanced allergenicity of birch pollen. PloS One 8, e80147. https://doi.org/10.1371/journal.pone.0080147.

Bell, M., Turrell, G., Beesley, B., Boruff, B., Trapp, G., Zubrick, S.R., Christian, H.E., 2020. Children's neighbourhood physical environment and early development: an ondividual child level linked data study. J. Epidemiol. Community Health 74, 321–329. https://doi.org/10.1136/jech-2019-212686.

Buters, J., Prank, M., Sofiev, M., Pusch, G., Albertini, R., Annesi-Maesano, I., et al., 2015. Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season. J. Allergy Clin. Immunol. 136, 87–95. https://doi.org/10.1016/j.jaci.2015.01.049.

Bobbink, R., Hicks, K., Galloway, J., Spranger, T., Alkemade, Ashmore, M., Bustamante, M., Cinderby, S., Davidson, E., Dentener, F., Emmett, B., Erisman, J.W., Fenn, M., Gilliam, F., Nordin, A., Pardo, L., De Vries, W., 2010. Global assessment of nitrogen deposition effects on terrestrial plant diversity: a synthesis. Ecol. Appl. 20, 30–59. https://doi.org/10.1890/08-1140.1.

Borlee, F., Yzermans, C.J., Aalders, B., Rooijackers, J., Krop, E., Maassen, C.B.M., Schellevis, F., Brunekreef, B., Heederik, D., Smit, L.A.M., 2017. Air pollution from livestock farms is associated with airway obstruction in neighboring residents. Am. J. Respir. Crit. Care Med. 196, 1152–1161. https://doi.org/10.1164/rccm.201701-0021oc.

Buteau, S., Shekarrizfard, M., Hatzopolou, M., Gamache, P., Liu, L., Smargiassi, A., 2020. Air pollution from industries and asthma onset in childhood: a population-based birth cohort study using dispersion modeling. Environ. Res. 185, 109180. https://doi.org/10.1016/j.envres.2020.109180.

Cariñanos, P., Casares-Porcel, M., Díaz de la Guardia, C., Aira, M.J., Belmonte, J., Boi, M., et al., 2017. Assessing allergenicity in urban parks: a nature-based solution to reduce the impact on public health. Environ. Res. 155, 219–227. https://doi.org/10.1016/j.envres.2017.02.015.

Cai, J., Li, B., Yu, W., Yao, Y., Wang, L., Li, B., Wang, Y., Du, C., Xiong, J., 2020. Associations of household dampness with asthma, allergies, and airway diseases among preschoolers in two cross-sectional studies in Chongqing, China: repeated surveys in 2010 and 2019. Environ. Int. 140, 105752. https://doi.org/10.1016/j.envint.2020.105752.

Carr, T.F., Bleecker, E., 2016. Asthma heterogeneity and severity. World Allergy Organ J 9, 41. https://doi.org/10.1186/s40413-016-0131-2.

Casas, L., Thomas, I., Nawrot, T.S., Bouland, C., Deboosere, P., Van Nieuwenhuyse, A., Nemery, B., 2015. Impact of green/blue spaces on specific morbidity and cause-specific mortality in Belgium: the GRESP-HEALTH project protocol (2015-2019). Arch. Publ. Health 73, P16. https://doi.org/10.1186/2049-3258-73-S1-P16.

Casas, L., Simons, K., Nawrot, T.S., Brasseur, O., Declerck, P., Buyl, R., Coomans, D., Nemery, B., Van Nieuwenhuyse, A., 2016. Respiratory medication sales and urban air pollution in Brussels (2005 to 2011). Environ. Int. 94, 576–582. https://doi.org/10.1016/j.envint.2016.06.019.

Cates, C., 2001. Chronic asthma. BMJ 323, 976. https://doi.org/10.1136/bmj.323.7319.976.

Ceulemans, T., Stevens, C.J., Duchateau, L., Jacquemyn, H., Gowing, D.J.G., Merckx, R., Wallace, H., van Rooijen, N., Goethem, T., Bobbink, R., Dorland, E., Gaudnik, C., Alard, D., Corcket, E., Muller, S., Dise, N.B., Dupré, C., Diekmann, M., Honnay, O., 2014. Soil phosphorus constrains biodiversity across European grasslands. Global Change Biol. 20, 3814–3822. https://doi.org/10.1111/gcb.12650.

D'Amato, G., Cecchi, L., Bonini, S., Nunes, C., Annesi-Maesano, I., Behrendt, H., Liccardi, G., Popov, T., van Cauwenberge, P., 2007. Allergenic pollen and pollen allergy in Europe. Allergy 62, 976–990. https://doi.org/10.1111/j.1398-9995.2007.01393.x.

D'Amato, G., Ortega, O.P.L., Annesi-Maesano, I., D'Amato, M., 2020. Prevention of allergic asthma with allergen avoidance measures and the role of exposome. Curr. Allergy Asthma Rep. 20, 8. https://doi.org/10.1007/s11882-020-0901-3.

Dadvand, P., Gascon, M., Markevych, I., 2019. Green spaces and child health and development. In: Marselle, M.R., Stadler, J., Korn, H., Irvine, K.N., Bonn, A. (Eds.), Biodiversity and Health in the Face of Climate Change. SpringerOpen, Cham, pp. 121–130. https://doi.org/10.1007/978-3-030-02318-8_6.

Dadvand, P., Villanueva, C.M., Font-Ribera, L., Martinez, D., Basagaña, X., Belmonte, J., Vrijheid, M., Gražulevičienė, R., Kogevinas, M., Nieuwenhuijsen, M.J., 2014. Risks and benefits of green spaces for children: a cross-sectional study of associations with sedentary behavior, obesity, asthma, and allergy. Environ. Health Perspect. 122, 1329–1335. https://doi.org/10.1289/ehp.1308038.

Dales, R.E., Cakmak, S., Burnett, R.T., Judek, S., Coates, F., Brook, J.R., 2000. Influence of ambient fungal spores on emergency visits for asthma to a regional children's hospital. Am. J. Respir. Crit. Care Med. 162, 2087–2090. https://doi.org/10.1164/ajrccm.162.6.2001020.

Damgaard, C., Jensen, L., Frohn, L.M., Borchsenius, F., Nielsen, K.E., Ejrnæs, R., Stevens, C.J., 2011. The effect of nitrogen deposition on the species richness of acid grasslands in Denmark: a comparison with a study performed on a European scale. Environ. Pollut. 159, 1778–1782. https://doi.org/10.1016/j.envpol.2011.04.003.

Dannemiller, K.C., Gent, J.F., Leaderer, B.P., Peccia, J., 2016. Indoor microbial communities: influence on asthma severity in atopic and nonatopic children. J. Allergy Clin. Immunol. 138, 76–83. https://doi.org/10.1016/j.jaci.2015.11.027 e1.

DePriest, K., Butz, A., Curriero, F.C., Perrin, N., Gross, D., 2019. Associations among neighborhood greenspace, neighborhood violence, and children's asthma control in an urban city. Ann. Allergy Asthma Immunol. 123, 608–610. https://doi.org/10.1016/j.anai.2019.10.003.

de Rooij, M.M.T., Smit, L.A.M., Erbrink, H.J., Hagenaars, T.J., Hoek, G., Ogink, N.W.M., Winkel, A., Heederik, D.J.J., Wouters, I.M., 2019. Endotoxin and particulate matter emitted by livestock farms and respiratory health effects in neighboring residents. Environ. Int. 132, 105009. https://doi.org/10.1016/j.envint.2019.105009.

Dewaelheyns, V., Elsen, A., Vandendriessche, H., Gulinck, H., 2013. Garden management and soil fertility in Flemish domestic gardens. Landsc. Urban Plann. 116, 25–35. https://doi.org/10.1016/j.landurbplan.2013.03.010.

Dewaelheyns, V., Rogge, E., Gulinck, H., 2014. Putting domestic gardens on the agenda using empirical spatial data: the case of Flanders. Appl. Geogr. 50, 132–143. https://doi.org/10.1016/j.apgeog.2014.02.011.

Diette, G.B., Markson, L., Skinner, E.A., Nguyen, T.T.H., Algatt-Bergstrom, P., Wu, A.W., 2000. Nocturnal asthma in children affects school attendance, school performance and parents' work attendance. Arch. Pediatr. Adolesc. Med. 154 https://doi.org/10.1001/archpedi.154.9.923, 923-923.

Donaldson, K., Gilmour, M.I., MacNee, W., 2000. Asthma and PM_{10}. Respir. Res. 1, 12–15. https://doi.org/10.1186/rr5.

Donovan, G.H., Gatziolis, D., Longley, I., Douwes, J., 2018. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. Nature Plants 4, 358–364. https://doi.org/10.1038/s41477-018-0151-8.

Ebmeier, S., Thayabaran, D., Braithwaite, I., Bénamara, C., Weatherall, M., Beasley, R., 2017. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). Lancet 390, 935–945. https://doi.org/10.1016/S0140-6736(17)31448-4.

Eguiluz-Gracia, I., Mathioudakis, A.G., Bartel, S., Vijverberg, S.J.H., Fuertes, E., Comberiati, P., Cai, Y.S., Tomazic, P.V., Diamant, Z., Vestbo, J., Galan, C., Hoffmann, B., 2020. The Need for Clean Air: the Way Air Pollution and Climate Change Allergic Rhinitis and Asthma. https://doi.org/10.1111/all.14177. Allergy.

Ehteshami-Afshar, S., FitzGerald, J.M., Doyle-Waters, M.M., Sadatsafavi, M., 2016. The global economic burden of asthma and chronic obstructive pulmonary disease. Int. J. Tubercul. Lung Dis. 20, 11–23. https://doi.org/10.5588/ijtld.15.0472.

Erbas, B., Lowe, A.J., Lodge, C.J., Matheson, M.C., Hosking, C.S., Hill, D.J., Vicendese, D., Allen, K.J., Abramson, M.J., Dharmage, S.C., 2013. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clin. Exp. Allergy 43, 3337–3343. https://doi.org/10.1111/cea.12071.

Erbas, B., Jazayeri, M., Lambert, K.A., Katelaris, C.H., Prendergast, L.A., Tham, R., Parrodi, M.J., Davies, J., Newbigin, E., Abranson, M.J., Dharmage, S.C., 2018. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: a systematic review and meta-analysis. Allergy 73, 1632–1641. https://doi.org/10.1111/all.13407.

Ferrante, G., Asta, F., Cilluffo, G., De Sario, M., Michelozzi, P., La Grutta, S., 2020. The effect of residential urban greenness on allergic respiratory diseases in youth: a narrative review. World Allergy Journal 13, 100096. https://doi.org/10.1016/j.waojou.2019.100096.

Flamant-Hulin, M., Annesi-Maesano, I., Caillaud, D., 2013. Relationships between molds and asthma suggesting non-allergic mechanisms. A rural-urban comparison. Pediatr. Allergy Immunol. 24, 345–351. https://doi.org/10.1111/pai.12082.

Francisco, P.W., Jacobs, D.E., Targos, L., Dixon, S.L., Breysse, J., Rose, W., Cali, S., 2017. Ventilation, indoor air quality, and health in homes undergoing weatherization. Indoor Air 27, 463–477. https://doi.org/10.1111/ina.12325.

Fuertes, E., Markevych, I., Thomas, R., Boyd, A., Granell, R., Mahmoud, O., Heinrich, J., Garcia-Aymerich, J., Roda, C., Henderson, J., Jarvis, D., 2020. Residential greenspace and lung function up to 24 years of age: the ALSPAC birth cohort. Environ. Int. 140, 105749. https://doi.org/10.1016/j.envint.2020.105749.

García-Mozo, H., 2017. Poaceae pollen as the leading aeroallergen worldwide: a review. Allergy 72, 1849–1858. https://doi.org/10.1111/all.13210.

Gernes, R., Brokamp, C., Rice, G.E., Wright, J.M., Kondo, M.C., Michael, Y.L., Donovan, G.H., Gatziolis, D., Bernstein, D., LeMasters, G.K., Lockey, J.E., Hershey, G. K.K., Ryan, P.H., 2019. Using high-resolution residential greenspace measures in an urban environment to assess risks of allergy outcomes in children. Sci. Total Environ. 668, 760–767. https://doi.org/10.1016/j.scitotenv.2019.03.009.

Gruffydd-Jones, K., Thomas, M., Roman-Rodríguez, M., Infantino, A., FitzGerald, J.M., Pavord, I., Haddon, J.M., Elsasser, U., Vogelberg, C., 2019. Asthma impacts on workplace productivity in employed patients who are symptomatic despite background therapy: a multinational survey. J. Asthma Allergy 12, 183–194. https://doi.org/10.2147/jaa.s204278.

Guilbert, T.W., Bacharier, L.B., Fitzpatrick, A.M., 2014. Severe asthma in children. J Allergy Clin Immunol Pract 2, 489–500. https://doi.org/10.1016/j.jaip.2014.06.022.

Guilbert, A., Cox, B., Bruffaerts, N., Hoebeke, L., Packeu, A., Hendrickx, M., De Cremer, K., Bladt, S., Brasseur, O., Van Nieuwenhuyse, A., 2018. Relationships between aeroallergen levels and hospital admissions for asthma in the Brussels-Capital Region: a daily time series analysis. Environ. Health 17, 35. https://doi.org/10.1186/s12940-018-0378-x.

Haahtela, T., Holgate, S., Pawankar, R., Akdis, C.A., Benjaponpitak, S., Caraballo, L., et al., 2013. The biodiversity hypothesis and allergic disease: world allergy organization position statement. World Allergy Org J 6, 3. https://doi.org/10.1186/1939-4551-6-3.

Hanski, I., von Hertzen, L., Fyhrquist, N., Koskinen, K., Torppa, K., Laatikainen, T., et al., 2012. Environmental biodiversity, human microbiota, and allergy are interrelated. Proc. Natl. Acad. Sci. U.S.A. 109, 8334–8339. https://doi.org/10.1073/pnas.1205624109.

Halken, S., 2004. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. Pediatr. Allergy Immunol. 15, 4–19. https://doi.org/10.1111/j.1399-3038.2004.0148b.x.

Hartley, K., Ryan, P., Brokamp, C., Gillespie, G.L., 2020. Effect of greenness on asthma in children: a systematic review. Publ. Health Nurs. 37, 453–460. https://doi.org/10.1111/phn.12701.

Hernández, A., Parrón, T., Alarcón, R., 2011. Pesticides and asthma. Curr. Opin. Allergy Clin. Immunol. 11, 90–96. https://doi.org/10.1097/ACI.0b013e3283445939.

Hughes, H.K., Matsui, E.C., Tschudy, M.M., Pollack, C.E., Keet, C.A., 2017. Pediatric asthma health disparities: race, hardship, housing, and asthma in a national survey. Acad Pediatr 17, 127–134. https://doi.org/10.1016/j.acap.2016.11.011.

Idrose, N.S., Dharmage, S.C., Lowe, A.J., Lambert, K.A., Lodge, C., Abramson, M.J., Douglass, J.A., Newbigin, E.J., Erbas, B., 2020. A systematic review of the role of grass pollen and fungi in thunderstorm asthma. Environ. Res. 181, 10891. https://doi.org/10.1016/j.envres.2019.108911.

James, P., Banay, R.F., Hart, J.E., Laden, F., 2015. A review of the health benefits of greenness. Curr. Epidemiol Rep 2, 131–142. https://doi.org/10.1007/s40471-015-0043-7.

Janssen, S., Dumont, G., Fierens, F., Mensink, C., 2008. Spatial interpolation of air pollution measurements using CORINE land cover data. Atmos. Environ. 42, 4884–4903. https://doi.org/10.1016/j.atmosenv.2008.02.043.

Kasprzyk, I., Cwik, A., Kluska, K., Wojcik, T., Cariñanos, P., 2019. Allergenic pollen concentrations in the air of urban parks in relation to their vegetation. Urban For Urban Greening 46, 126486. https://doi.org/10.1016/j.ufug.2019.126486.

Khreis, H., Kelly, C., Tate, J., Parslow, R., Lucas, K., Nieuwenhuijsen, M.J., 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ. Int. 100, 1–31. https://doi.org/10.1016/j.envint.2016.11.012.

Kim, K.H., Kabir, E., Jahan, S.A., 2020. Exposure to pesticides and the associated human health effects. Sci. Total Environ. 575, 525–535. https://doi.org/10.1016/j.scitotenv.2016.09.009.

Kleijn, D., Kohler, F., Baldi, A., Batary, P., Concepcion, E.D., Clough, Y., Diaz, M., Gabriel, D., Holzschuh, A., Knop, E., Kovacs, A., Marshall, E.J.P., Tscharntke, T., Verhulst, J., 2009. On the relationship between farmland biodiversity and land-use intensity in Europe. Proc Roy Soc B Biol Sci 276, 903–909. https://doi.org/10.1098/rspb.2008.1509.

Lambert, K.A., Bowatte, G., Tham, R., Lodge, C., Prendergast, L., Heinrich, J., Abramson, M.J., Dharmage, S.C., Erbas, B., 2017. Residential greenness and allergic respiratory diseases in children and adolescents - a systematic review and meta-analysis. Environ. Res. 159, 212–221. https://doi.org/10.1016/j.envres.2017.08.002.

Lambert, K.A., Lodge, C., Lowe, A.J., Prendergast, L.A., Thomas, P.S., Bennett, C.M., Abramson, M.J., Dharmage, S.C., Erbas, B., 2019. Pollen exposure at birth and adolescent lung function, and modification by residential greenness. Allergy 74, 1977–1984. https://doi.org/10.1111/all.13803.

Lara, B., Rojo, J., Fernández-González, F., Pérez-Badia, R., 2019. Prediction of airborne pollen concentrations for the plane tree as a tool for evaluating allergy risk in urban green areas. Landsc. Urban Plann. 189, 285–295. https://doi.org/10.1016/j.landurbplan.2019.05.002.

Linneberg, A., Petersen, K.D., Hahn-Pedersen, J., Hammerby, E., Serup-Hansen, N., Boxall, N., 2016. Burden of allergic respiratory disease: a systematic review. Clin. Mol. Allergy 14, 12. https://doi.org/10.1186/s12948-016-0049-9.

Lundbäck, B., Backman, H., Lötvall, J., Rönmark, E., 2016. Is asthma prevalence still increasing? Expet Rev. Respir. Med. 10, 39–51. https://doi.org/10.1586/17476348.2016.1114417.

Lunjani, N., Satitsuksanoa, P., Lukasik, Z., Sokolowska, M., Eiwegger, T., O'Mahony, L., 2018. Recent developments and highlights in mechanisms of allergic diseases: microbiome. Allergy 73, 2314–2327. https://doi.org/10.1111/all.13634.

Lovasi, G.S., Quinn, J.W., Neckerman, K.M., Perzanowski, M.S., Rundle, A., 2008. Children living in areas with more street trees have lower prevalence of asthma. J. Epidemiol. Community Health 62, 647–649. https://doi.org/10.1136/jech.2007.071894.

Lovasi, G.S., O'Neil-Dunne, J.P.M., Lu, J.W.T., Sheehan, D., Perzanowski, M.S., MacFaden, S.W., King, K.L., Matte, T., Miller, R.L., Hoepner, L.A., Perera, F.P., Rundle, A., 2013. Urban tree canopy, and asthma, wheeze, rhinitis, and allergenic sensitization to tree pollen in a New York city Birth Cohort. Environ. Health Perspect. 121, 494–500. https://doi.org/10.1289/ehp.1205513.

Lefebvre, W., Vranckx, S., 2013. Validation of the IFDM-model for use in urban applications, study accomplished in the framework of the ATMOSYS-project. VITO report 2013/RMA/R/56. Available online at: http://www.atmosys.eu/faces/doc/ATMOSYS_Deliverable_10_IFDM_Model_Validation.pdf.

Liu, A.H., Babineau, D.C., Krouse, R.Z., Zoratti, E.M., Pongracic, J.A., O'Connor, G.T., et al., 2016. Pathways through which asthma risk factors contribute to asthma severity in inner-city children. J. Allergy Clin. Immunol. 138, 1042–1050. https://doi.org/10.1016/j.jaci.2016.06.060.

Markevych, I., Schoierer, J., Hartig, T., Chudnovsky, A., Hystad, P., Dzhambov, A.M., et al., 2017. Exploring pathways linking greenspace to health: theoretical and methodological guidance. Environ. Res. 158, 301–317. https://doi.org/10.1016/j.envres.2017.06.028.

Meftaul, I.M., Venhateswarlu, K., Dharmarajan, R., Annamalai, P., Megharaj, M., 2020. Pesticides in the urban environment: a potential threat that knocks at the door. Sci. Total Environ. 711, 134612. https://doi.org/10.1016/j.scitotenv.2019.134612.

Milligan, K.L., Matsui, E., Sharma, H., 2016. Asthma in urban children: epidemiology, environmental risk factors, and the public health domain. Curr. Allergy Asthma Rep. 16, 33. https://doi.org/10.1007/s11882-016-0609-6.

Mnich, C., Weyland, S., Jekauc, D., Schipperijn, J., 2019. Psychosocial and physiological health outcomes of green exercise in children and adolescents-a systematic review. Int. J. Environ. Res. Publ. Health 16, 4266. https://doi.org/10.3390/ijerph16214266.

Murrison, L.B., Brandt, E.B., Myers, J.B., Hershey, G.K.K., 2019. Environmental exposures and mechanisms in allergy and asthma development. J. Clin. Invest. 129, 1504–1515. https://doi.org/10.1172/JCI124612.

O'Lenick, C.R., Winquist, A., Chang, H.W., Kramer, M.R., Mulholland, J.A., Grundstein, A., Sarnat, S.E., 2017. Evaluation of individual and area-level factors as modifiers of the association between warm-season temperature and pediatric asthma morbidity in Atlanta, GA. Environ. Res. 156, 132–144. https://doi.org/10.1016/j.envres.2017.03.021.

Orellano, P., Quaranta, N., Reynoso, J., Balbi, B., Vasquez, J., 2017. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. PloS One 12, e0174050. https://doi.org/10.1371/journal.pone.0174050.

Papi, A., Brightling, C., Pedersen, S.E., Reddel, H.K., 2018. Asthma. Lancet 391, 173–800. https://doi.org/10.1016/S0140-6736(17)33311-1.

Parajuli, A., Hui, N., Puhakka, R., Oikarinen, S., Grönroos, M., Selonen, V.A.O., et al., 2020. Yard vegetation is associated with gut microbiota composition. Sci. Total Environ. 713, 136707. https://doi.org/10.1016/j.scitotenv.2020.136707.

Parmes, E., Pesce, G., Sabel, C.E., Baldacci, S., Bono, R., Brescianini, S., et al., 2020. Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: evidence from 9 European cohorts. Environ. Res. 183, 108953. https://doi.org/10.1016/j.envres.2019.108953.

Patrick, D.M., Sbihi, H., Dai, D.L.Y., Al Mamun, A., Rasali, D., Rose, C., et al., 2020. Decreasing antibiotic use, the gut microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30052-7 (in press).

Pavilonis, B.T., Sanderson, W.T., Merchant, J.A., 2013. Relative exposure to swine animal feeding operations and childhood asthma prevalence in an agricultural cohort. Environ. Res. 122, 74–80. https://doi.org/10.1016/j.envres.2012.12.008.

Payne, R., Dise, N.B., Field, C., Dore, A.J., Caporn, S.J.M., Stevens, C.J., 2017. Nitrogen deposition and plant biodiversity: past, present, and future. Front. Ecol. Environ. 8, 431–436. https://doi.org/10.1002/fee.1528.

Pierangeli, I., Nieuwenhuijsen, M.J., Cirach, M., Rojas-Rueda, D., 2020. Health equity and burden of childhood asthma - related to air pollution in Barcelona. Environ. Res. https://doi.org/10.1016/j.envres.2019.109067 (in press):109067.

Raney, M.A., Hendry, C.F., Yee, S.A., 2019. Physical activity and social behaviors of urban children in green playgrounds. Am. J. Prev. Med. 56, 522–529. https://doi.org/10.1016/j.amepre.2018.11.004.

Rook, G.A., 2013. Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. Proc. Natl. Acad. Sci. U.S.A. 110, 18360–18367. https://doi.org/10.1073/pnas.1313731110.

Rugel, E.J., Henderson, S.B., Carpiano, R.M., Brauer, M., 2017. Beyond the normalized difference vegetation index (NDVI): developing a natural space index for population-level health research. Environ. Res. 159, 474–483. https://doi.org/10.1016/j.envres.2017.08.033.

Ruokolainen, L., Fyhrquist, N., Haahtela, T., 2016. The rich and the poor: environmental biodiversity protecting from allergy. Curr. Opin. Allergy Clin. Immunol. 16, 421–426. https://doi.org/10.1097/aci.0000000000000304.

Sahni, S., Talwar, A., Khanijo, S., Talwar, A., 2017. Socioeconomic status and its relationship to chronic respiratory disease. Adv Respir Med 85, 97–108. https://doi.org/10.5603/arm.2017.0016.

Sbihi, H., Tamburic, L., Koehoorn, M., Brauer, M., 2015. Greenness and incident childhood asthma: a 10-year follow-up in a population-based birth cohort. Am. J. Respir. Crit. Care Med. 192, 1131–1133. https://doi.org/10.1164/rccm.201504-0707LE.

Sbihi, H., Boutin, R.C., Cutler, C., Suen, M., Finlay, B.B., Turvey, S.E., 2019. Thinking bigger: how early-life environmental exposures shape the gut microbiome and influence the development of asthma and allergic disease. Allergy 74, 2103–2115. https://doi.org/10.1111/all.13812.

Son, J.Y., Kim, H., Bell, M.L., 2015. Does urban land-use increase risk of asthma symptoms? Environ. Res. 142, 309–318. https://doi.org/10.1016/j.envres.2015.06.042.

Squillacioti, G., Bellisario, V., Levra, S., Piccioni, P., Bono, R., 2019. Greenness availability and respiratory health in a population of urbanised children in North-Western Italy. Int. J. Environ. Res. Publ. Health 17, 108. https://doi.org/10.3390/ijerph17010108.

Strand, L.B., Tsai, M.K., Wen, C.P., Chang, S.S., Brumpton, B.M., 2018. Is having asthma associated with an increased risk of dying from cardiovascular disease? A prospective cohort study of 446 346 Taiwanese adults. BMJ Open 8, e019992. https://doi.org/10.1136/bmjopen-2017-019992.

Sullivan, P., Ghushchyan, V.G., Navaratnam, P., Friedman, H.S., Kavati, A., Ortiz, B., Lanier, B., 2018. School absence and productivity outcomes associated with childhood asthma in the USA. J. Asthma 55, 161–168. https://doi.org/10.1080/02770903.2017.1313273.

Sullivan, K., Thakur, N., 2020. Structural and social determinants of health in asthma in developed economies: a scoping review of literature published between 2014 and 2019. Curr Allergy Ashtma Rep 20, 5. https://doi.org/10.1007/s11882-020-0899-6.

Tattersall, M.C., Evans, M.D., Korcarz, C.E., Mitchell, C., Anderson, E., DaSilva, D.F., Salazar, L.P., Gern, J.E., Jackson, D.J., Lemanske, R.F., Stein, J.H., 2018. Asthma is associated with carotid arterial injury in children: the Childhood Origins of Asthma (COAST) Cohort. PloS One 13, e0204708. https://doi.org/10.1371/journal.pone.0204708.

Tétreault, L.F., Doucet, M., Gamache, P., Fournier, M., Brand, A., Kosatsky, T., Smargiassi, A., 2016. Childhood exposure to ambient air pollutants and the onset of asthma: an administrative cohort study in Québec. Environ. Health Perspect. 124, 1276–1282. https://doi.org/10.1289/ehp.1509838.

Tham, R., Katelaris, C.H., Vicendese, D., Dharmage, S.C., Lowe, A.J., Bowatte, G., Taylor, P., Burton, P., Abramson, M.J., Erbas, B., 2017. The role of outdoor fungi on asthma hospital admissions in children and adolescents: a 5-year time stratified case-crossover analysis. Environ. Res. 154, 42–49. https://doi.org/10.1016/j.envres.2016.12.016.

Tham, R., Erbas, B., Dharmage, S.C., Tang, M.L.K., Aldakheel, F., Lodge, C.J., Thomas, P. S., Taylor, P.E., Abramson, M.J., Lowe, A.J., 2019. Outdoor fungal spores and acute respiratory effects in vulnerable individuals. Environ. Res. 178, 108675. https://doi.org/10.1016/j.envres.2019.108675.

Tillmann, S., Tobin, D., Avison, W., Gilliland, J., 2018. Mental health benefits of interactions with nature in children and teenagers: a systematic review. J. Epidemiol. Community Health 72, 958–966. https://doi.org/10.1136/jech-2018-210436.

Tischer, C., Gascon, M., Fernández-Somoano, A., Tradón, A., Materola, A., Ibarluzea, J., et al., 2017. Urban green and grey space in relation to respiratory health in children. Eur. Respir. J. 49, 1502112. https://doi.org/10.1183/13993003.02112-2015.

Trabelsi, S., Casas, L., Nemery, B., Nawrot, T.S., Thomas, I., 2019. Geographies of asthma medication purchase for pre-schoolers in Belgium. Respir. Res. 20, 90. https://doi.org/10.1186/s12931-019-1052-8.

Twohig-Bennett, C., Jones, A., 2018. The health benefits of the great outdoors: a systematic review and meta- analysis of greenspace exposure and health outcomes. Environ. Res. 166, 628–637. https://doi.org/10.1016/j.envres.2018.06.030.

van den Bosch, M., Sang, A.O., 2017. Urban natural environments as nature-based solutions for improved public health – a systematic review of reviews. Environ. Res. 158, 373–384. https://doi.org/10.1016/j.envres.2017.05.040.

Van Herck, M., Spruit, M.A., Burtin, C., Djamin, R., Antons, J., Goërtz, Y.M.J., Ebadi, Z., Janssen, D.J.A., Vercoulen, J.H., Peters, J.B., Thong, M.S.Y., Otker, J., Coors, A., Sprangers, M.A.G., Muris, J.W.M., Wouters, E.F.M., van 't Hul, A.J., 2018. Fatigue is highly prevalent in patients with asthma and contributes to the burden of disease. J. Clin. Med. 7, 471. https://doi.org/10.3390/jcm7120471.

Vandenplas, O., Vinnikov, D., Blanc, P.D., Agache, I., Bachert, C., Bewick, L., Cardell, L. O., Cullinan, P., Demoly, P., Descatha, A., Fonseca, J., Haahtela, T., Hellings, P.W., Jamart, J., Jantunen, J., Ö, Kalayci, Price, D., Samolinski, B., Sastre, J., Tian, L., Valero, A.L., Zhang, X., Bousquet, J., 2018. Impact of rhinitis on work productivity: a systematic review. J Allergy Clinical Immunol Pract 6, 1274–1286. https://doi.org/10.1016/j.jaip.2017.09.002.

Wang, J., Zhao, Z., Zhang, Y., Li, B., Huang, C., Zhang, X., Deng, Q., Lu, C., Qian, H., Yang, X., Sun, Y., Sundell, J., Norbäck, D., 2019. Asthma, allergic rhinitis and eczema among parents of preschool children in relation to climate, and dampness and mold in dwellings in China. Environ. Int. 130, 104910. https://doi.org/10.1016/j.envint.2019.104910.

WHO, 2017. Asthma. https://www.who.int/en/news-room/fact-sheets/detail/asthma. (Accessed 23 January 2019).

Wood, E., Harsant, A., Dallimer, L., Cronin de Chavez, A., McEachan, R.R.C., Hassall, C., 2018. Not all green space is created equal : biodiversity predicts psychological restorative benefits from urban green space. Front. Psychol. 9, 2320. https://doi.org/10.3389/fpsyg.2018.02320.

Ziska, L.H., Gebhard, D.E., Frenz, D.A., Faulkner, S., Singer, B.D., Straka, J.G., 2003. Cities as harbingers of climate change: common ragweed, urbanization, and public health. J. Allergy Clin. Immunol. 111, 290–295. https://doi.org/10.1067/mai.2003.53.

https://statbel.fgov.be/sites/default/files/files/opendata/Statistische/sectoren/Secteurs/stat-NL_tcm325-174181.pdf, 2019–. (Accessed 3 July 2020).