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Residential greenness and allergic respiratory diseases in children and adolescents – A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Background: The aetiology of allergic respiratory disease in children is not yet fully understood. Environmental factors are believed to play a major part. The amount of green vegetation surrounding the home (residential greenness) has been recently identified as a potentially important exposure

Objectives: Our goal was to provide a systematic review and quantitative summary of the evidence regarding the relationship between residential greenness and allergic respiratory diseases in children.

Methods: Peer-reviewed literature published prior to 1 March 2017 was systematically searched using nine electronic databases. Meta-analyses were conducted if at least three studies published risk estimates for the same outcome and exposure measures.

Results: We included 11 articles across broad outcomes of asthma and allergic rhinitis. Reported effects were inconsistent with varying measures to define residential greenness. Only limited meta-analysis could be conducted, with the pooled odds ratios for asthma (OR 1.01 95%CI 0.93, 1.09; I^2 68.1%) and allergic rhinitis (OR 0.99 95%CI 0.87, 1.12; I^2 72.9%) being significantly heterogeneous.

Conclusions: Inconsistencies between the studies were too large to accurately assess the association between residential greenness and allergic respiratory disease. A standardised global measure of greenness which accounts for seasonal variation at a specific relevant buffer size is needed to create a more cohesive body of evidence and for future examination of the effect of residential greenness on allergic respiratory diseases.

1. Introduction

Allergic respiratory diseases are an important public health problem in children globally. The prevalence of asthma and allergic rhinitis has increased rapidly over the last 50 years (Asher et al., 2006). While the rates are stabilising in developed countries (Chawla et al., 2012), they are still increasing in many other countries including Latin America and China (Pearce et al., 2007). Persistent allergic rhinitis and uncontrolled severe asthma can significantly impair the quality of life of affected individuals (Guilbert et al., 2011; Meltzer, 2001; Silva et al., 2015). Allergic respiratory diseases place a substantial economic burden on society (Barnett and Nurmagambetov, 2011) and the families of affected children (Bahadori et al., 2009).

Although the causes of allergic respiratory diseases in children are not yet fully understood, environmental factors are key contributors to these epidemics. Traffic related air pollutants (TRAP) have been implicated in the development of asthma and sensitisation to aeroallergens (Bowatte et al., 2015), as well as exacerbations of existing respiratory conditions in children (Evans et al., 2014; Li et al., 2011). Exposure to both outdoor fungal spores and pollen have been shown to increase exacerbations of existing asthmatic patients (Cakmak et al., 2002; Erbas et al., 2012; Pongracic et al., 2010) and of incident asthma and allergic rhinitis (Erbas et al., 2013).

Recently there has been great interest in the amount of green vegetation surrounding the home (residential greenness) as a potential environmental component in the aetiology of allergic respiratory

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diseases. The literature has been inconsistent, with some studies reporting benefits associated with an increase in greenness and others finding the opposite. Reduced asthma prevalence was associated with an increase in street tree density in New York City (Lovasi et al., 2008). Reduced odds of incident asthma during pre-school years were associated with an increases in the Normalized Difference Vegetation Index (NDVI) within 100 m around the participants' homes (Sbihi et al., 2015). Others have reported adverse effects, such as an increase in risk of asthma with increased NDVI within 100 m around the participants' homes (Andrusaityte et al., 2016) or percentage green space as determined by Light Detection and Ranging (LiDAR) imagery within 250 m around the participants' homes (Lovasi et al., 2013). No published systematic reviews have assessed the role of residential greenness on allergic respiratory diseases in children and adolescents.

The aim of this systematic review and meta-analysis was to synthesise the current literature to assess whether surrounding residential greenness was an important factor associated with allergic respiratory diseases in children and adolescents.

2. Methods

2.1. Search strategy

The literature was systematically searched using the following bibliographic databases: Medline, EMBASE, CINAHL, AMED, Scopus, Informit Health, Web of Science, ProQuest central and Google Scholar for English language peer reviewed original articles. Given the lack of consensus on how to measure residential greenness, an extensive list of search terms was used (Table S1). Further hand searches were conducted using citations from included publications.

2.2. Inclusion criteria and definitions

We included cohort, case-control, cross-sectional and ecological studies. Specific inclusion criteria ensured selection of human studies whose study population comprised of children and adolescents aged less than 18 years of age. Outcome measures included asthma, wheeze, allergic rhinitis or lung function. In all cases, multiple definitions including doctor diagnosis, self-report and hospital records data were considered. For inclusion, the studies must have defined the exposure metric and reported on the relationship between residential greenness and at least one of the outcome measures.

2.3. Selection of included articles

The abstracts of all identified papers were independently reviewed for initial inclusion by KL and GB; then full papers were read by KL and GB to determine if all inclusion criteria were met. If disagreement arose between reviewers, the paper was referred to a third reviewer (BE) for assessment.

2.4. Data extraction

Data extraction in each article included was performed by KL in a standardised manner. This process was duplicated by GB. Data were extracted from each article included: author, year of publication, type of study, study population/country, number of children in sample, age range, exposure definition, season of exposure measurement, allergic respiratory disease(s) assessed, outcome definition, risk estimates along with 95%CI/p value, confounders and any interactions assessed.

2.5. Assessment of quality and risk of bias

A validated quality assessment framework (Zaza et al., 2000) was adapted to assess and rate the design, execution (threats to validity and reliability), generalisability, risk of bias and reporting of each study. Individual study quality was assessed using a checklist that categorised and graded: study design; description of the study population and how they were selected; how exposure and outcome were measured and whether these were valid and reliable; the appropriateness of the statistical testing and controlling for study design effects; identification and controlling for potential bias (selection, measurement, recall and analytical biases related to sample size, buffer zones and statistical methods) and potential confounders (season, air pollution, aeroallergens, socioeconomic status, parental atopy, biodiversity of vegetation, nature of built environment); and whether problems with data analysis limited interpretation of the results. Quality assessment data were extracted independently by two authors (KL and RT) (Scoring Matrix included in supplement E1). The quality assessment of this scale is based on the selection of study sample, outcome assessment, exposure assessment and adjustment for confounders.

The assessment of overall risk of bias across all the studies was guided by the GRADE guidelines for rating the quality of the evidence and study limitations of observational studies. Risk of bias in each individual study was categorised from none to high risk of bias in order to assess overall biases and limitations in this research field (Guyatt et al., 2011).

2.6. Standardisation of data

To ensure consistency in the interpretation of effect sizes from different studies, quantitative synthesis was focused on the odds of a given outcome for an increase in residential greenness. To enable comparisons across studies the effect sizes used to generate the meta-analysis estimate were scaled and standardised into the same magnitude (0.1 increase in NDVI) for those studies where NDVI was used. We were unable to do this for studies with different metrics for residential greenness and they were excluded from the meta-analysis.

2.7. Meta-analysis methods

Statistical software R version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria Foundation for R Foundation for Statistical Computing, Vienna, Austriatatistical Computing, Vienna, Austria) and the package 'metafor' (Viechtbauer, 2010) was used to perform meta-analyses. Given that this review includes studies measuring a number of different allergic respiratory disease outcomes, a threshold number of three studies measuring the same outcome with the same exposure was chosen in order to decide whether to conduct a meta-analysis on a particular outcome. In the meta-analysis, the effect related to the most common exposure buffer was selected. To estimate pooled effect sizes and 95% Confidence Intervals, random effects models were used. I^2 statistics (Higgins and Thompson, 2002) were calculated as measures of between study heterogeneity. A high value of I^2 meant that most of the variability across studies was due to heterogeneity rather than chance, pooling results with an I^2 above 80% was not recommended (Higgins and Thompson, 2002).

Statistical software STATA version 14.1 (Stata Corp LP, College Station, TX, USA) was used to create forest plots of these analyses.

3. Results

The electronic literature search and hand searching found 484 peer-reviewed scientific articles after duplicate papers were removed (Fig. 1). Of these, 463 were excluded following review of titles and abstracts. A large number of these papers were not relevant to the role of residential greenness on childhood allergic respiratory diseases or were conference abstracts, commentary articles or reviews of other articles. Of the remaining 21 articles, 10 were excluded following full-text assessment as they did not assess the relevant exposures (residential greenness) and health outcomes (any form of allergic respiratory disease) in the defined study population (children and/or

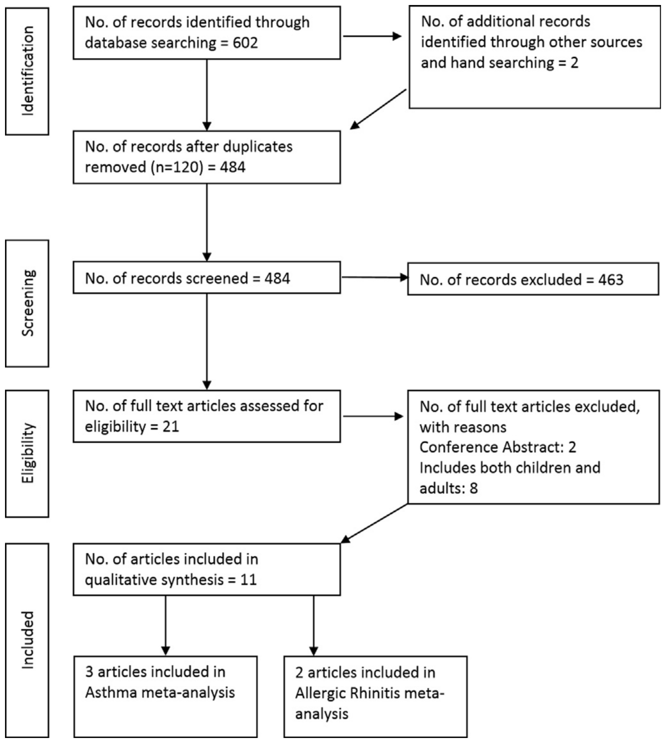

Fig. 1. PRISMA flow diagram.

adolescents).

3.1. Characteristics of included studies

In total 11 papers were included in this review and their characteristics are summarised in Table 1. The 11 included articles represented 11 cohorts (7 articles including 2 nested case-control studies), 1 cross-sectional (1 article) and 3 ecological studies (3 articles). Five of the 11 cohort studies were conducted in Europe (Andrusaityte et al., 2016; Fuertes et al., 2014b, 2016), five in the US and Canada (Brokamp et al., 2016; Fuertes et al., 2016; Lovasi et al., 2013; Sbihi et al., 2015, 2017) and one in Australia (Fuertes et al., 2016). The cross-sectional sample came from Europe (Dadvand et al., 2014). Two of the ecological studies were conducted in the US (Lovasi et al., 2008; Pilat et al., 2012) and one was conducted in 94 countries around the world (Fuertes et al., 2014a).

3.2. Quality assessment and risk of bias

The overall methodological quality of the studies was high for observational studies, with most studies scoring ≥ 75%. The other two studies scored 39% and 43%. The sample size was too small to detect a meaningful difference in one study with 11 data points (Pilat et al., 2012) which also contained an inconsistent exposure mesurement. Convenience sampling was used by one study (Lovasi et al., 2008) and the outcome measure not well defined.

3.3. Exposure assessment

A number of different metrics were used to define the surrounding residential greenness, with the most common being the Normalized Difference Vegetation Index (NDVI) (Andrusaityte et al., 2016; Brokamp et al., 2016; Dadvand et al., 2014; Fuertes et al., 2014a, b, 2016; Pilat et al., 2012; Sbihi et al., 2015, 2017). The NDVI is a Geographic Information Systems (GIS) measure of area-level greenness that has been validated for use in epidemiological studies (Rhew et al., 2011) and is derived from publicly available satellite images. The index calculation is based on the ratio of visible (red) and near-infrared light reflection off the land surface (Weier and Herring, 2000). NDVI values range between −1 and 1 with low values (below 0.1) corresponding to areas of barren rock, sand, or snow and high values (> 0.6) to temperate and tropical rainforests (Weier and Herring, 2000). While these studies all use the same scale of measurement, NDVI was averaged across a buffer of anywhere from 100 m to 59 km depending on the study. One study utilised a combined high-resolution Light Detection and Ranging (LiDAR) data, colour infrared aerial imagery and ancillary vector data to assess the percentage of residential greenness in the form of tree canopy cover around the home (Lovasi et al., 2013).

Another study did not use remote imaging to assess the surrounding residential greenness, instead using street tree density derived from the New York Parks and Recreation Department Street Tree Census as a measure of greenness (Lovasi et al., 2008). Street tree density was calculated by taking the total number of trees on street segments (counted by census-takers) within the area divided by land area.

3.4. Outcome assessment

3.4.1. Asthma

The most common method of classifying children as asthmatics was by parental report of doctor diagnosis. The Brief Respiratory Questionnaire (Bonner et al., 2006) was used in one study (Lovasi et al., 2013) and the validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire in two studies (Andrusaityte et al., 2016; Dadvand et al., 2014). Dadvand and colleagues required wheezing or having used asthma medication in the preceding 12 months for children to be defined as having 'current asthma'. Pilat et al. (2012) also required a dual response with parents answering yes to both "Has a physician/medical care provider ever told you that this child has asthma?" and "Does this child still have asthma?" to be defined as asthmatic. This was then normalized and mapped to the area unit to produce a childhood asthma rate per area.

Brokamp et al. (2016) used a mix of self-report and clinical testing, defining asthmatic children as those who self-reported symptoms of asthma and had either bronchial hyper-reactivity (> 12% increase in FEV_1 following bronchodilation) or a positive MCCT (PC_{20} ≤ of 4 mg/ml methacholine concentration).

Sbihi et al. (2015) used linked administrative records to define asthma with children who had ≥ 2 physician visits in a rolling 12-month period and/or ≥ 1 inpatient hospitalisation for asthma. This definition was also used in their later work (Sbihi et al., 2017) where they subsequently used group based modelling to define four asthma trajectories: No Asthma, Transient Asthma, Late-Onset Chronic Asthma and Early-Onset Chronic Asthma. One article (Lovasi et al., 2008) used secondary data for asthma prevalence and hospital admission, but did not clearly define how this was determined.

3.4.2. Allergic rhinitis

Definitions of allergic rhinitis varied. Three studies relied on parental report of doctor diagnosis (Fuertes et al., 2014b, 2016; Lovasi et al., 2013) while two (Fuertes et al., 2016) defined allegic rhinitis based on a diagnosis during a physician assessment at a follow-up visit. One of the seven birth cohorts investigated by Fuertes et al. (Fuertes et al., 2016) considered either parental report of a medical diagnosis of allergic rhinitis or allergic rhinitis symptoms after exposure to furred pets or pollen sufficient for a classification of allergic rhinitis.

Parental report of symptoms (sneezing, or a runny, or blocked nose accompanied by itchy watery eyes without a cold or the flu) was used to define allergic rhinitis or allergic rhino-conjunctivitis in three articles (Dadvand et al., 2014; Fuertes et al., 2014a, 2016). Fuertes et al. (2014a) futher classified the children into intermittent and persistent rhinitis symptoms by asking in which of the past 12 months the nose problem occurred. Rates were then calculated on a per centre basis. One study (Fuertes et al., 2016) considered either one or more episodes of

Table 1
Characteristics of included studies.

Author (Year)	Location	Number of children in the sample	Study design	Exposure measure	Allergic respiratory disease assessed		Age range	
					Asthma	Allergic Rhinitis	Exposure measure	Outcome measure
Lovasi et al. (2008)	New York City, USA	Unknown.	Ecological	Street tree density	X		Perinatal	4 to 5
Pilat et al. (2012)	Texas, USA	Unknown.	Ecological	NDVI	X		At outcome measure	0 to 17
Lovasi et al. (2013)	New York, USA (CCCEH)	n = 549	Population based birth cohort	LiDAR imagery	X	X	Perinatal	5 and 7
Dadvand et al. (2014)	Sabadell, Spain	n = 3178	Cross-sectional sample	NDVI	X	X	At outcome measure	9 to 12
Fuertes et al. (2014a)	Global - ISAAC Phase 3 study population	n = 642,313	Ecological	NDVI		X	At outcome measure	13 to 14
Fuertes et al. (2014b)	Two German birth cohorts - GINIplus and LISAplus	n = 5803	Population based birth cohorts	NDVI		X	At outcome measure	10
Sbihi et al. (2015).	Vancouver, Canada	n = 51,857	Nested Case-Control	NDVI	X		Perinatal	0 to 5 5 to 10
Andrusaityte et al. (2016)	Lithuania (KANC)	n = 1489	Nested Case-Control	NDVI	X		At outcome measure	4 to 6
Brokamp et al. (2016)	Cincinnati, USA (CCAAPS)	n = 762	High-Risk birth cohort	NDVI	X		Multiple	7
Fuertes et al. (2016).	Seven birth cohorts (Swedish (BAMSE), Australian (MACS), Dutch (PIAMA), Canadian (CAPPS and SAGE), and German (GINIplus and LISAplus))	n = 13,016	Population based birth cohorts (BAMSE, PIAMA, SAGE, LISAplus, GINIplus) and High-Risk birth cohorts (MACS, CAPPS)	NDVI		X	Birth	6 to 8 10 to 12
Sbihi et al. (2016).	Vancouver, Canada	n = 65,254	Population based birth cohort	NDVI	X		Perinatal	0 to 10 (Trajectory modelling)

NDVI: Normalized Difference Vegetation Index.
LiDAR: Light Detection and Ranging.

Table 2a
Characteristics of studies examining effect of residential greenness on outcomes related to asthma.

Author (Year)	Exposure definition	Outcome definition	Exposure estimate (95% CI)	Other variables included in the models as confounders	Interactions
Lovasi et al. (2008)	Street tree density (total number of trees on street segments within the UHF divided by land area)	Prevalence of asthma Hospitalisation for asthma	RR per SD of tree density Prevalence of asthma: 0.71 (0.64, 0.79) Hospitalisations as a result of asthma: 0.89 (0.75, 1.06)	Sociodemographic characteristics, population density and proximity to pollution sources	None
Pilat et al. (2012)	Average NDVI per MSA in the months of April - June 2006	Current asthma rates	A Pearson's product–moment correlation for the average NDVI and the residual asthma variable. Reported as not significant.	Relative humidity, temperature, ozone, particulate matter, and ethnicity	Canopy cover %
Lovasi et al. (2013)	Urban tree canopy coverage (combined high-resolution Light Detection and Ranging (LiDAR) data and colour infrared aerial imagery) for address at time of birth (250 m).	Current asthma (assessed by BQR questionnaire) at 5 and 7 years old.	Relative risk (RR) increase per standard deviation of tree canopy coverage: 5 years 1.11 (0.85, 1.45) 7 years 1.17 (1.02, 1.33)	Sex, age, ethnicity, maternal asthma, previous birth, other previous pregnancy, Medicaid, tobacco smoke in home, active maternal smoking, population density, % poverty, % park land, and estimated traffic volume.	None
Dadvand, et al. (2014)	Residential surrounding greenness (NDVI at 100, 250, 500 and 1000 m areas of current residential address)	Current asthma (asthma as assessed using the ISAAC questionnaire plus having had wheezing or having used asthma medication in the preceding 12 months)	Per IQR increase in NDVI (OR): 100 m: 1.00 (0.82, 1.21) 250 m: 1.00 (0.78, 1.27) 500 m: 1.03 (0.79, 1.34) 1000 m: 1.06 (0.85, 1.32)	Child's sex and age, exposure to environmental tobacco smoke at home, having older siblings, type of school (public vs. private), parental education, and parental history of asthma	SES (school type, parental education, Urban Vulnerability index) – data not shown.
Sbihi et al. (2015).	Surrounding Greenness (NDVI) during the perinatal period. (Measured in 100 m areas around residential postal codes)	1. incident asthma during preschool-age (0–5 years) 2. incident asthma during school years (6–10 years)	per interquartile (0.11) NDVI increase (OR): Pre-school aged: 0.96 (0.93–0.99) School aged reported as no association.	Maternal age at delivery, parity, breastfeeding status at discharge, birth weight, gestational period, household income, and maternal education.	Co-exposures to air pollutants and road proximity, term birth weight, maternal education, household income (neighbourhood level), distance to nearest park, gestational length
Andrusaityte et al. (2016)	Residential surrounding greenness (mean NDVI at 100, 300 and 500 m areas of exact residential address)	Clinically diagnosed asthma (International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire completed by parents)	Per IQR increase in NDVI (OR): 100 m: 1.43 (1.10, 1.85) 300 m: 1.23 (0.94, 1.61) 500 m: 1.18 (0.88, 1.57) For above median NDVI (OR): 100 m: 1.19 (0.79, 1.79) 300 m: 1.17 (0.78, 1.76) 500 m: 1.39 (0.92, 2.10)	Mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat in the past 12 months, living in a flat, yearly mean of ambient PM2.5 & NO2.	Proximity to park greater than 1 ha (binary outcome: live within 1000 m of a park)
Brokamp et al. (2016)	NDVI at 400 m around home address from a single image in June 2000, for each address recorded over the first seven years of life.	Having asthma – recorded by a combination of self-reported symptoms of asthma and had either bronchial hyper-reactivity (> 12% increase in FEV1 following bronchodilation) or a positive MCCT (PC20 ≤ of 4 mg/ml methacholine concentration)	NDVI at birth address: OR: 0.14 (0.02, 1.19) NDVI at 7 yr address: OR: 0.18 (0.02, 1.70) Mean NDVI over all addresses: OR: 0.15 (0.01, 2.04)	None	None
Sbihi et al. (2016).	Surrounding Greenness (NDVI) during the perinatal period. (Measured in 100 m areas around residential postal codes)	Asthma trajectory defined based on group-based trajectory modelling (No asthma, transient, Late-Onset and Early-Onset) – risk compared to being in 'no asthma' group	Highest quartile of NDVI to lowest: Transient: 0.91 (0.80, 1.05) Late-Onset: 1.05 (0.90, 1.23) Early-Onset: 1.01 (0.81, 1.25) Second highest quartile of NDVI to lowest: Transient: 0.98 (0.86, 1.11) Late-Onset: 1.29 (1.12, 1.49) Early-Onset: 1.15 (0.94, 1.41)	Gender, parity, breastfeeding initiation, birth weight, delivery mode, maternal smoking and educational attainment, and household income	None

NDVI: Normalized Difference Vegetation Index.
LiDAR: Light Detection and Ranging.

hay fever in last 12 months and/or use of any treatment to hay fever sufficient for a classification of allergic rhinitis.

3.5. Investigating outcomes related to asthma (Table 2a)

Five studies (2 nested case-control studies, 2 birth cohorts and 1 cross-sectional study) investigated the association between residential greenness and asthma as a dichotomous (yes/no) outcome. Two ecological studies examined asthma in terms of prevalence rate in a defined area. One article investigated asthma trajectory defined based on group-based trajectory modelling (refer to Table 2a). The same group of children was investigated twice by Sbihi et al. (2015, 2017), first as a case control and then investigating asthma trajectories.

Six of these studies used NDVI as the exposure measurement. A case control study (Sbihi et al., 2015) observed a decrease risk of asthma amongst pre-school aged children (0–5 years) related to an increase in NDVI at 100 m. This effect was not observed amongst school aged children (6–10 years). Further adjustment for co-exposure to air pollution (NO, NO_2 and $PM_{2.5}$) and road proximity (within 50 m or 150 m of a highway or 50 m or within 150 m of major road) individually, did not alter the findings.

However, a case control study of children who did not move in the first 4–6 years of life (Andrusaityte et al., 2016) showed an increase in the odds of asthma per IQR increase in NDVI with a buffer size of 100 m. This increase was no longer significant when the buffer size was increased to 300 or 500 m. NDVI at 400 m also showed no significant association with asthma in children in Cincinnati, USA (Brokamp et al., 2016), irrespective of whether address at birth or at time of outcome measure was used. A cross-sectional study of 3178 school children age 9–12 in Spain found no significant effects (Dadvand et al., 2014) with exposure measures of NDVI in 100 m, 250 m, 500 m and 1000 m buffers around the current home address.

An ecological study compared mean NDVI per Metropolitan Statistical Area (MSA) to the asthma rate of the same area (Pilat et al., 2012). They found average NDVI was not correlated with asthma ($r = 0.052$, p-value $= 0.88$) after adjustment for ethnicity, relative humidity, temperature, ozone and particulate matter.

Sbihi et al. (2017) found a slight protective effect of the highest levels of residential greenness being associated with a decreased risk of a transient asthma trajectory relative to the non-asthma trajectory. This decrease was not robust and disappeared when the covariates of gender, parity, breastfeeding initiation, birth weight, delivery mode, maternal smoking and educational attainment, and household income were added into the model. Their work also showed an increase in risk of late onset chronic asthma relative to the non-asthma trajectory for those in the second highest greenness quartile (RR: 1.29 95%CI: 1.12–1.49) after adjustment.

LiDAR was used by one study (Lovasi et al., 2013) which found residential greenness to be detrimental in a prospective cohort of Dominican and African-American children born in New York. They showed an increase in risk of asthma diagnosis at age 7 years (RR: 1.17; 95%CI 1.02–1.33) related to an increase in residential greenness at 250 m.

A significant decrease in prevalence of asthma was found amongst 4–5 year olds (RR 0.71; 95%CI 0.64–0.79) when using street tree density as a measure of surrounding residential greenness, after accounting for sociodemographic characteristics, population density and proximity to pollution sources (Lovasi et al., 2008).

The three studies (2 case control and 1 cross-sectional) which used the same measure of residential greenness exposure (NDVI at a buffer of 100 m) (Andrusaityte et al., 2016; Dadvand et al., 2014; Sbihi et al., 2015) were meta-analysed after standardisation. The meta-analysis showed no significant overall association between asthma and residential greenness (pooled OR: 1.01 95%CI: 0.93–1.09, Fig. 2). This result was significantly heterogeneous ($I^2 = 68.1\%$, p-value $= 0.02$), and the heterogeneity persisted after the removal of the cross-sectional study (results not shown). Due to lack of study numbers, we were unable to stratify according to age group or consider the effects of confounding variables for which the studies had adjusted.

3.6. Investigating outcomes related to allergic rhinitis (Table 2b)

Four articles, reporting 8 cohorts and a cross-sectional study, have investigated the effect of residential greenness on individual allergic rhinitis (Dadvand et al., 2014; Fuertes et al., 2014b, 2016; Lovasi et al., 2013). In some of these studies, multiple cohorts were used to increase the statistical power to detect significant effects (Fuertes et al., 2014b, 2016). One article (Fuertes et al., 2014a) used an ecological analysis to investigate the mean difference in country-level prevalence of intermittent and persistent rhinitis (refer to Table 2b).

NDVI was used as the exposure measurement in all but one study. Dadvand and colleagues (Dadvand et al., 2014) cross-sectional study found no significant effects of residential greenness on allergic rhinoconjunctivitis with exposure measures of NDVI at 100 m, 250 m, 500 m and 1000 m buffers. They adjusted for a number of confounders (child's sex and age, exposure to environmental tobacco smoke at home, having older siblings, type of school (public vs. private), parental education, and parental history of asthma) and conducted a stratified analysis considering markers of socio-economic status which did not show associations.

Two German cohorts - GINI/LISA North and South – have been investigated twice. In 2014, Fuertes et al. (2014b) investigated the effect of mean NDVI in 500 m residential buffers on doctor diagnosis of allergic rhinitis in children aged 3–10 years. GINI/LISA South showed no significant effect of residential greenness (OR 1.16 95%CI; 0.99–1.36) while the GINI/LISA North showed a decrease in the odds of allergic rhinitis with an increase in mean NDVI (OR 0.75; 95%CI 0.60–0.93). NDVI interacted significantly with the study area to produce this heterogeneous result.

Analysed further in 2016 as part of a seven cohort study (Fuertes et al., 2016), the data were age stratified and the exposure effect was standardised to a 0.2 increase in NDVI. GINI/LISA North showed a decrease in odds of allergic rhinitis aged 10–12 years (OR 0.63; 95%CI 0.41–0.98). GINI/LISA South showed no significant effect of residential greenness at age 10–12 years (OR 1.26 95%CI 0.93–1.70) and an increase in odds amongst those aged 6–8 (OR 1.69 95%CI 1.19–2.41). The other cohorts included in the study (Fuertes et al., 2016) showed similar inconsistencies, resulting in a pooled odds ratio of 1.00 (95%CI 0.69–1.45) amongst children aged 6–8 and a pooled odds ratio of 0.96 (95%CI 0.71–1.30) amongst children aged 10–12. They also stratified by sex and age, showing a non-significant decline in the odds of allergic rhinitis in girls aged 6–8 (OR: 0.87 95%CI: 0.51–1.48) and a similar non-significant increase in the odds of allergic rhinitis in boys of the same age (OR: 1.15 95%CI: 0.76–1.74).

One ecological study used the ISAAC Phase 3 study population employing data from 222 centres in 94 countries (Fuertes et al., 2014a). They analysed the effect of mean NDVI – mapped at 59 km^2 around each participating centre – on the mean difference in country-level prevalence of intermittent and persistent rhinitis per 100 children. The mean difference reported was not significant.

Utilising LiDAR, Lovasi et al. (2013) reported no association between residential greenness and rhinitis at age five (RR: 1.60; 95%CI: 0.79–3.22) or age 7 (RR: 1.40; 95%CI 0.63–3.08).

As the exposure metric of NDVI at a 500 m buffer was common to more than 2 cohorts and the age group effect sizes were presented, we conducted a meta-analysis (Fig. 3) for children aged 9–12 pooling results from Fuertes et al. (2016) and Dadvand et al. (2014). However, the pooled estimate (OR: 0.99 95%CI: 0.87–1.12) was significantly heterogeneous ($I^2 = 72.9\%$, p-value < 0.01).

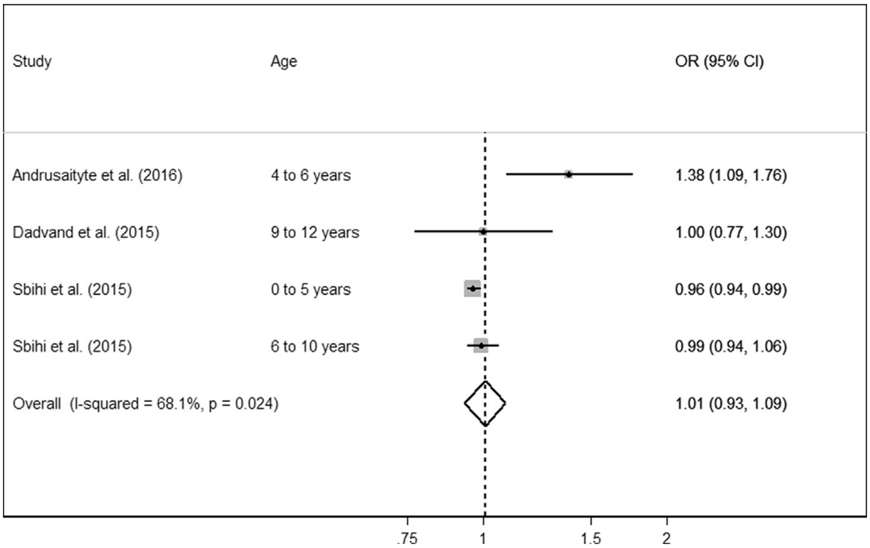

Fig. 2. Meta-analysis of asthma – all Ages.

4. Discussion

This is the first systematic review and meta-analysis assessing a possible association between residential greenness and allergic respiratory diseases in children and adolescents. For asthma, we found eight articles with two (1 ecological, 1 nested case-control) studies showing a protective effect of residential greenness, two (1 cohort, 1 nested case-control) studies showing a detrimental effect and four (1 ecological, 2 cohort, 1 cross-sectional) studies reporting no association. Our meta-analysis showed no significant overall association between residential greenness and asthma, but it was highly heterogeneous. Investigating allergic rhinitis we found five articles including a study of seven prospective birth cohorts. Again variable effects were found and our meta-analysis showed no significant overall association between residential greenness and allergic rhinitis.

A key issue in these studies was the assessment and definition of the outcome. For asthma and allergic rhinitis the assessment varied from parental or self-report, to administrative records to clinical assessment. Questionnaire wording for the self-report outcome varied substantially and definition varied from ever having a doctor-diagnosis to symptoms or treatment in the last 12 months. This variation in the assessment of the outcome impacted on the ability to develop a cohesive body of evidence, treating as the same outcome resulted in high heterogeneity and inconsistent study results. The limited number of studies did not allow us to break down the outcome variables further.

Another key issue is the measurement of the exposure. Nine studies used NDVI as the metric of residential greenness. In terms of global usability and comparability, NDVI is useful as it is a standardised global measure available at multiple time points. However it is a relatively crude measure when considering allergic outcomes, as it does not distinguish between types of vegetation. The NDVI reported from a landscape full of highly allergenic vegetation such as grasses and a relatively benign landscape may be identical, if the amount of green foliage is the same. Only one study used LiDAR imagery (Lovasi et al., 2013) to assess residential greenness. While standardised and globally applicable, unlike NDVI, LiDAR imagery is not freely available to the public and therefore not used by many investigators.

The spatial buffer selected to measure residential greenness also varied between studies with most choosing a buffer from 100 m up to 59 km, generally a prior selection to represent either the immediate environment, the neighbourhood environment or the city's environment. Furthermore, studies differed in how they scaled the effect estimates of residential greenness, with some giving estimates for an increase equal to the interquartile range of the data (Dadvand et al., 2014; Sbihi et al., 2015), others per standard deviation of the data (Lovasi et al., 2013), whilst others used a standardised 0.2 increase (Fuertes et al., 2016). Some studies chose to dichotomise their measure of residential greenness using cut point such as 'above median' (Andrusaityte et al., 2016). These factors made it difficult draw comparisons across the different studies.

Furthermore, residential greenness is a seasonal variable fluctuating greatly in some areas of the world. This particularly impacts on satellite derived measures such as the NDVI. An NDVI calculated from images taken during the summer months could be vastly different to one calculated from images taken during winter/spring (Fig. S1, Didan, 2015). Only three of the nine studies utilising NDVI as a measure of greenness attempted to control for this factor by calculating monthly averages (Fuertes et al., 2014a) or calculating an average for the year (Sbihi et al., 2015, 2017). The remaining studies using NDVI calculated residential greenness based on a single cloud free image for the each cohort/area. Spring (Dadvand et al., 2014; Pilat et al., 2012) and summer (Andrusaityte et al., 2016; Brokamp et al., 2016; Fuertes et al., 2016) were the most common seasons from which to calculate NDVI, although justification for the choice was rarely given. Even in the large study of seven cohorts (Fuertes et al., 2016) NDVI was calculated in different seasons across the included cohorts, with four cohorts (BAMSE, GINI +, LISA + and SAGE) being calculated during summer and three (CAPPS, MACS, PIAMA) during spring at birth. They also compared NDVI at ten years of age, again calculated from a single image taken during the autumn (BAMSE, PIAMA), summer (CAPPS, GINI +, LISA + and SAGE) or spring (MACS) months. This is a major problem due to the seasonality of greenness. Depending on the climatic conditions and vegetation profile there can be extreme differences in greenness between autumn and spring. While multiple images would be preferred, either averaged or as repeated measures, studies could have considered adjusting for season or time of outcome measure.

Seasonality of exposure measurement is particularly important when considering other environmental factors such as pollen. High pollen levels have been linked to an increase in paediatric ED presentations for asthma (Darrow et al., 2012; Erbas et al., 2012; Gleason et al., 2014; Ito et al., 2015) and hospital admissions (Chen et al., 2016). Early exposure to high pollen levels has also been implicated in the development of allergic respiratory disease (Erbas et al., 2013) and increased risk of asthma hospitalisation (Lowe et al., 2012). Pollen types and concentrations vary widely depending on location, season and meteorological conditions (D'Amato et al., 2007) and therefore could potentially explain some of the variation reported. While intact pollen grains, being 10–100 μm in diameter depending on the species,

Table 2b
Characteristics of studies examining effect of residential greenness on outcomes related to allergic rhinitis.

Author (Year)	Exposure definition	Outcome definition	Exposure estimate (95% CI)	Other variables included in the models as confounders	Interactions
Lovasi et al. (2013)	Urban tree canopy coverage (combined high-resolution Light Detection and Ranging (LiDAR) data, colour infrared aerial imagery and ancillary vector data) for address at time of birth (250 m) and at 5 and 7 years old (1000 m).	Current rhinitis (assessed by ISSAC questionnaire) at 5 and 7 years old.	Relative risk (RR) increase per standard deviation of tree canopy coverage 5 years 1.60 (0.79, 3.22) 7 years 1.40 (0.63, 3.08)	Sex, age, ethnicity, maternal asthma, previous birth, other previous pregnancy, Medicaid, tobacco smoke in home, active maternal smoking, population density, % poverty, % park land, and estimated traffic volume.	None
Dadvand et al. (2014)	Residential surrounding greenness (NDVI at 100, 250, 500 and 1000 m areas of current residential address)	Current allergic rhinoconjunctivitis (ISAAC questionnaire)	Per IQR increase in NDVI (OR): 100 m: 0.97 (0.88, 1.08) 250 m: 0.98 (0.87, 1.12) 500 m: 1.03 (0.90, 1.18) 1000 m: 1.05 (0.94, 1.18)	Child's sex and age, exposure to environmental tobacco smoke at home, having older siblings, type of school (public vs. private), parental education, and parental history of asthma	SES (school type, parental education, Urban Vulnerability index) – data not shown.
Fuertes et al. (2014a)	NDVI mapped to 0.07° × 0.07° grid, averaged across centre grid and 8 surrounding grids (approximately 59 km^2). Calculated for mean, maximum, minimum, SD and maximal difference of NDVI	Mean difference in country-level prevalence of intermittent and persistent rhinitis per 100 children	mean difference per increase of mean NDVI by 0.1 Intermittent rhinitis: 8.03 (−8.75 to 24.81) Persistent rhinitis: 9.45 (−3.84 to 22.75)	GNI per capita, population density, and climate type	Temperature (data not shown)
Fuertes et al. (2014b)	Residential greenness in a 500 m buffer around the 10-year home addresses (NDVI)	Doctor diagnosis of allergic rhinitis (yearly, from 3 to 10 years)	Allergic rhinitis (OR) per increase in mean NDVI: 1.03 (0.89, 1.19)	Age, sex, parental history of atopy, older siblings, maternal smoking during pregnancy, tobacco smoke exposure in the home (birth—4 years), cohort and parental education	Cohort (South: OR 1.16 (0.99, 1.36) & North: OR 0.75 (0.60, 0.93) PM2.5 mass; NO2; Population density.
Fuertes et al. (2016)	Mean NDVI at 500 m and 1000 m circular buffers around home address (age 6–8 and 10–12) taken during the spring and summer months of year of birth.	Allergic rhinitis defined based on a diagnosis during a physician assessment at a follow-up visit (CAPPS and SAGE) or parental report of a doctor's diagnosis (GINIplus and LISAplus) or parental symptom report (PIAMA and BAMSE) or either parental symptom or treatment report (MACS).	OR per 0.2 unit increase in mean NDVI Age 6–8: BAMSE: 1.42 (1.13, 1.79) CAPPS: 0.63 (0.32, 1.24) GINI/LISA North: 0.61 (0.36, 1.01) GINI/LISA South: 1.69 (1.19, 2.41) PIAMA: 0.67 (0.47, 0.95) SAGE: 1.31 (0.81, 2.12) Pooled estimate: 1.00 (0.69, 1.45) Age 10–12: BAMSE: 1.32 (1.07, 1.64) GINI/LISA North: 0.63 (0.41, 0.98) GINI/LISA South: 1.26 (0.93, 1.70) MACS: 0.96 (0.59, 1.57) PIAMA: 0.71 (0.53, 0.97) Pooled estimate: 0.96 (0.71, 1.30)	Adjusted for sex, age, parental atopy (not included for MACS), older siblings, maternal smoking during pregnancy, secondhand smoke exposure in the home (not available for MACS), socioeconomic status, group (CAPPS, GINI/LISA North and GINI/LISA South, MACS and PIAMA), region (CAPPS and PIAMA) and cohort (GINI/LISA North and GINI/LISA South)	Child sex, NO2 and population density tertiles, an urban/rural indicator and moving behaviour

NDVI: Normalized Difference Vegetation Index.
LiDAR: Light Detection and Ranging.

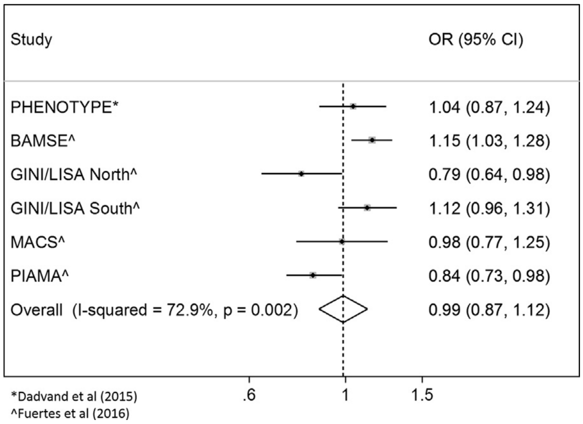

Fig. 3. Meta-analysis of allergic rhinitis – 9–12 years.

only penetrate into the airways in small amounts (Driessen and Quanjer, 1991), pollen allergens are also released in starch granules which being smaller, are much more readily inhaled (Bacsi et al., 2006; Visez et al., 2015). No study adjusted analysis based on level or type of pollen or included it as potential effect modifier.

Distance to roads should also be considered when investigating residential greenness. Trees along roadsides can trap air pollution and decrease the air quality in the immediate vicinity (Vos et al., 2013). Only one study (Sbihi et al., 2015) adjusted for distance to highways and major roads. Despite finding no significant interaction, the protective effect of residential greenness was enhanced in models including distance to highways and major roads. The granules of pollen released along major roadways bind to airborne particles such as diesel-exhaust (Behrendt and Becker, 2001). This interaction with air pollution increases the risk of sensitisation and exacerbations within children who are sensitised (D'Amato et al., 2007). The immune response to the allergen can also be modified by traffic related air pollutants (Fröhlich-Nowoisky et al., 2016). While fine particulate matter can change the allergen presentation, gaseous pollutants can increase inflammatory and immune responses to allergens (Sénéchal et al., 2015). Four studies (Fuertes et al., 2014b; Pilat et al., 2012; Sbihi et al., 2015, 2017) controlled or adjusted for some form of traffic related air pollution. As with proximity to roads, Sbihi and colleagues (Sbihi et al., 2015) showed an enhanced protective effect of residential greenness when NO, NO_2 or $PM_{2.5}$ was included in the model.

The difference between planned urban vegetation and diverse wild vegetation is a key component of the biodiversity hypothesis of allergy (Haahtela et al., 2013). Two of the studies considered the impact of urbanisation on residential greenness (Fuertes et al., 2014b, 2016). The study of two German cohorts split into geographical areas with GINI/LISA South being metropolitan and GINI/LISA North being more rural (Fuertes et al., 2014b) also found different effects with a decrease in odds of allergic rhinitis and atopic sensitisation present in the rural area and not the metropolitan. The interaction between the urban/rural regions within these studies and NDVI was significant and remained after adjustment for modifiers.

Due to the heterogeneity of outcomes and exposures measured and the small number of studies investigating residential greenness and allergic respiratory disease, only limited meta-analyses could be conducted. Differences in the age range of participants between studies contributed to the heterogeneity, with some studies not reporting age strata (Pilat et al., 2012). The sample size of the included studies varied significantly with some being quite small e.g. 11 (Pilat et al., 2012). In addition to the different measures used; NDVI at different buffers, LiDAR and street tree counting, the timing of measurement varied greatly within studies. Some considered greenness around the home ‘at birth’, generally within one or two years of child's birth, while others considered time of the outcome measurement. A standardised global measure of greenness – be it NDVI or percentage green space derived from LiDAR imaging – at a set buffer, during an appropriate time period, would have created a more cohesive body of evidence allowing for the greater examination of the effect of residential greenness on allergic respiratory diseases.

In summary, had we better exposure measures that considered potentially critical environmental confounders, we would have a better understanding of the role of residential greenness to allergic respiratory disease in children and adolescents. Further evidence of an effect of residential greenness may provide better insights into how better to manage day to day asthma and allergic diseases. With substantial population growth and migration to developed countries, more and more people are living in urbanised areas. Attention needs to be paid not just to the aesthetic qualities of the built environment, but the implications on public health when developing housing and surrounding green spaces.

Conflict of interest

Michael Abramson holds investigator initiated research grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has also received assistance with conference attendance from Sanofi. All other authors report no conflict of interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.08.002.

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