\$ SUPER

Contents lists available at ScienceDirect

Environmental Research

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





Effects of residential greenness during pregnancy on childhood asthma, rhinitis, eczema, and their comorbidity: findings from the French mother-child cohort Pélagie

Alan R. Patlán-Hernández a, ©, Christine Monfort , Etienne Audureau b, Marta Cirach c, e, Ralph Epaud f, g, & Kees de Hoogh h, ©, Sophie Lanone , Parisa Montazeri c, e, e, Danielle Vienneau h, Charline Warembourg o, Cécile Chevrier o, Marine Savouré a, Bénédicte Jacquemin a, **, 1 ©

- a Univ Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail), UMR_S 1085, F-35000, Rennes, France
- ^b Assistance Publique-Hôpitaux de Paris AP-HP, Hôpital Henri Mondor, Unité de Recherche Clinique (URC Mondor), Créteil, France
- ^c Institute for Global Health, Barcelona, Spain
- ^d Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain
- ^e CIBER Epidemiología y Salud Pública (CIBERESP), Spain
- f Centre Hospitalier Intercommunal de Créteil, Service de Pédiatrie Générale, Créteil, France
- g Centre des Maladies Respiratoires Rares (RESPIRARE), Créteil, France
- ^h Swiss Tropical and Public Health Institute, Kreuzstrasse 2, 4123, Allschwil, Switzerland
- i University of Basel Petersplatz 1 Postfach 4001 Basel Switzerland
- ^j Univ Paris Est Créteil, INSERM, IMRB, F-94010, Créteil, France

ARTICLE INFO

Keywords: Greenness Asthma Rhinitis Eczema Children

Degree of urbanization

ABSTRACT

Maternal exposure to residential greenness during pregnancy may influence childhood respiratory and allergic diseases development. Yet, evidence is limited and results are not consistent, furthermore most studies focus on urban areas. In a predominantly rural population, we aimed to assess the effect of maternal residential greenness during pregnancy on childhood asthma, rhinitis, eczema, and their comorbidity. We analyzed data from 1325 to 1119 participants in the 6- and 12-year follow-ups of the Pélagie mother-child cohort in Brittany, France. Ever asthma, rhinitis, and eczema were defined using validated questionnaires, and a multimorbidity phenotype was constructed. Greenness was assessed using the Normalized Difference Vegetation Index (NDVI) within a 300m buffer around the residential address. Adjusted logistic regressions per 0.1-unit increase in NDVI were performed, further stratifying by urban and rural areas. At inclusion, 78 % of mothers were non-smokers, 64 % lived in rural areas, and their average age was 30 ± 4 years; 50 % of children were boys. Median NDVI differed significantly between urban (0.45) and rural (0.57) areas (p = < 0.0001). Asthma, rhinitis, and eczema prevalence were respectively around 10 %, 20 %, and 20 % at both follow-ups. Overall, the NDVI within 300m did not show significant associations at either follow-up, across the whole study population, except for eczema (0.87 (0.76-1.00), p=0.05), and the single-disease category of the multimorbidity phenotype (0.87, (0.76-0.99),p=0.03) at 6 years, where it showed protective associations. Our findings highlight the need for further research, particularly in rural populations, to clarify the relationship between prenatal residential greenness and childhood health outcomes.

 $\textit{E-mail addresses:} \ a lan-ricardo. pat lanhernan dez @univ-rennes. fr \ (A.R.\ Pat lán-Hernán dez), \ benedicte. jacquemin @inserm. fr \ (B.\ Jacquemin).$

^{*} Corresponding author. Institut de recherche en santé, environnement et travail (IRSET) 9 Av. du Professeur Léon Bernard, 35000, Rennes, France.

^{**} Corresponding author.

 $^{^{1}}$ Co-last authors.

1. Introduction

Global prevalence of chronic respiratory and allergic diseases has increased over the past few decades, maintaining them among the most prevalent chronic health conditions affecting both adults and children (Pawankar, 2014; Soriano et al., 2020; Shin et al., 2023). In 2021, these diseases contributed to an estimated of 108.5 million Years Lived with Disability (DALYs) across all age groups, including 3.1 million DALYs among children aged 5-14 years (Institute for Health Metrics and Evaluation). Among these chronic conditions, asthma, rhinitis, and eczema are the most common during childhood, with global prevalence estimates around 8-11 %, 9-23 % and 8-35 %, respectively (Garcia-Aymerich et al., 2015; García-Marcos et al., 2022; The Global Asthma Report, 2022, 2022). Moreover, coexistence of these diseases is frequent. Different studies have estimated that childhood prevalence of asthma, rhinitis, and eczema multimorbidity, defined as the coexistence of at least two of these conditions, range from 4 to 50 % (Gough et al., 2015; Sigurdardottir et al., 2021). Similar trends have been observed in France. A nationwide survey estimated the prevalence of childhood asthma at approximately 11 % among six-year-olds between 2012 and 2013 (Delmas et al., 2017). Among children from 8 to 9 years, data from the PARIS cohort showed that 13.1 % of them had been diagnosed with asthma, 37.6 % with eczema, and 6.3 % with hay fever, with 9.9 % experiencing allergic multimorbidity (Momas et al., 2022). Additionally, stage 2 of the ISAAC-France survey reported comparable prevalence rates among children aged 9-11 years: 13 % for asthma, 23 % for rhinitis, and 25 % for eczema (Sasso et al., 2019).

The increase in the prevalence of these diseases parallels the trend for people to live in increasingly urban areas (D'Amato et al., 2015; Murrison et al., 2019; Celebi et al., 2022). This results in a greater exposure to urban factors such as traffic-related air pollution or noise, and reduced access to natural spaces, which can have adverse health effects (Murrison et al., 2019). Urban green spaces could be a mitigating solution, as green spaces could limit the effects of air pollution, noise, or heat islands (Markevych et al., 2017; Gunawardena et al., 2017; Wong et al., 2021), and literature supports the beneficial effects of exposure to green space on several health outcomes such as birth outcomes, cardiovascular diseases, and mental health (Twohig-Bennett and Jones, 2018; Yang et al., 2021; Hu et al., 2021). Nevertheless, evidence of the effects of green space on respiratory and allergic outcomes remains inconclusive as studies show contrasting results (Squillacioti et al., 2024). Indeed, meta-analyses that considered the effect of exposure to green space via the Normalized Difference Vegetation Index (NDVI), a greenness indicator, found no significant pooled effects of the NDVI on childhood asthma or allergic rhinitis, overall showing low to moderate heterogeneity among studies ($I^2 \ge 25$ %) (Squillacioti et al., 2024; Wang et al., 2023; Cao et al., 2023). As highlighted by Squillacioti et al. the inconsistency of findings may not only reflect the variability of methodological approaches across studies but also the heterogeneity and complexity of the relationship between greenness and respiratory health and allergies (Squillacioti et al., 2024). One factor that could contribute to the complexity of the effects of greenness is urbanicity, as there are differences between urban and rural areas in terms of the type, use, size, accessibility, and composition of green spaces (Jarvis et al., 2020; Hartig et al., 2020; García de Jalón et al., 2021) and areas, as captured by the NDVI. Urban green spaces are typically represented by urban parks and gardens, whereas rural green spaces are mainly represented by agricultural fields, and natural landscapes such as woodlands, forests, and grasslands (Taylor and Hochuli, 2017). However, very few studies have investigated the effects of greenness in rural areas as the majority of studies on children's respiratory health and allergies have been predominantly or exclusively carried out in urban populations (Squillacioti et al., 2024; Wang et al., 2023).

In line with the developmental origins of health and disease (DOHaD) hypothesis, the prenatal period may represent a particular window of vulnerability, with long-term consequences for the child's

subsequent development (Dadvand et al., 2019). However, studies considering exposure to greenness during pregnancy are scarce, we identified only 13 published studies examining the association between green space exposure during pregnancy and childhood asthma, rhinitis, or eczema. Of these, 9 investigated its impact on asthma, 5 on rhinitis, and 2 on eczema (Kuiper et al., 2020; Stanescu et al., 2024; Fernandes et al., 2024; Sbihi et al., 2015; Maritano et al., 2022; Shiroshita et al., 2024; Yang et al., 2024; Rantala et al., 2024; Mansouri et al., 2024; Lin et al., 2022; Abellan et al., 2024; Lovasi et al., 2013; Paciência et al., 2023). Among the 11 studies using the residential NDVI during pregnancy as the greenness indicator (Kuiper et al., 2020; Stanescu et al., 2024; Fernandes et al., 2024; Sbihi et al., 2015; Shiroshita et al., 2024; Yang et al., 2024; Rantala et al., 2024; Mansouri et al., 2024; Lin et al., 2022; Abellan et al., 2024; Paciência et al., 2023), most yielded non-significant results (Kuiper et al., 2020; Fernandes et al., 2024; Shiroshita et al., 2024; Lin et al., 2022; Abellan et al., 2024; Paciência et al., 2023), but the results were heterogeneous between studies. Moreover, only two studies took into account the urbanicity of participants (Shiroshita et al., 2024; Yang et al., 2024). One linked greenness to childhood asthma, showing deleterious effects in metropolitan areas but non-significant results in non-metropolitan areas (Shiroshita et al., 2024). The other, adjusting for urbanicity, found protective effects on rhinitis but deleterious effects on allergic rhinitis (Yang et al., 2024).

In light of these gaps, we aimed to investigate the associations of maternal exposure to surrounding residential greenness during pregnancy with the prevalence of childhood asthma, rhinitis, eczema, and their comorbidity, and whether these associations differ between urban and rural settings. For this, we used data from a French mother-child cohort with a predominantly rural population. We hypothesize that higher exposure to greenness during pregnancy is associated with a lower prevalence of childhood asthma, rhinitis, eczema, and their comorbidity, and that these associations could differ between rural and urban areas.

2. Methods

2.1. Study population

The Pélagie (Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance) study, fully described in a previous publication (Warembourg et al., 2024), is a mother-child cohort that enrolled 3421 pregnant women in Brittany, France, from 2002 to 2006.

Participants were eligible for recruitment if they attended a consultation with a midwife, gynecologist, obstetrician, or sonographer before 19 weeks of gestation, and if they planned to give birth in the Brittany region. During their initial consultation, health practitioners informed the pregnant women about the study's objectives, obtained their written consent, provided them with a study kit (which included a questionnaire and urine sampling materials), and transmitted their contact information to the research team. The women completed the questionnaire at home and mailed it to the laboratory (Inserm U1085) (Warembourg et al., 2024). Information collected through the inclusion questionnaire included the parents' family and health history, diet, lifestyle, and sociodemographic characteristics. All participants provided informed consent, and the study procedures were approved by French ethics committees.

At birth, 3322 liveborn singletons were eligible for follow-up. Medical information on pregnancy, delivery, and the newborn's health were gathered from midwives, pediatricians, and hospital records. During the 2-, 6- and 12-year follow-ups, self-administered questionnaires, sent and returned by mail, were completed by the parents (mainly the mothers) gathering information on the demographic characteristics, health status, lifestyle, and immediate environment of the family. For the present study we use data only from the inclusion and the 6- and 12-year follow-up questionnaires. We excluded 1) newborns with major congenital

malformations (n=100) as defined by the EUROCAT definition (EUROCAT Special Report, 2012), 2) extremely, very, and moderately preterm births (<34 weeks of gestation, n=43) as studies have shown a higher risk of respiratory pathologies in premature children (Gutvirtz et al., 2022), and 3) participants living in departments outside the Brittany region (n=38).

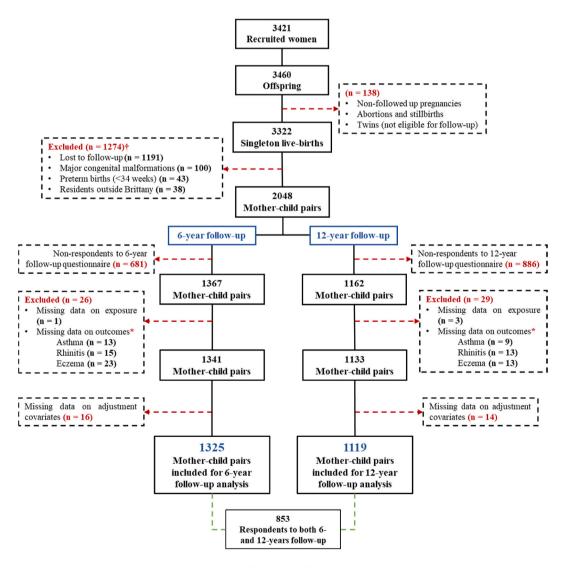
Separate analyses were conducted for participants at the 6- and 12-year follow-ups. This resulted in a population of 1367 participants for the 6-year follow-up and 1162 for the 12-year follow-up. Subsequently, participants with non-geocoded addresses during pregnancy or missing data on outcomes and covariates at the 6-year (n = 42) and 12-year (n = 43) follow-ups were excluded. In total, 1325 mother-child pairs were included in the 6-year follow-up analysis, and 1119 were included in the 12-year follow-up analysis. Of these, 853 mother-child pairs participated in both follow-ups.

A flowchart of the selection process for the analysis population is shown in Fig. 1. The geographical distribution during pregnancy of the mother-child pairs included for analyses is illustrated in Fig. S1.

2.2. Exposure assessment

Participants' surrounding residential greenness was estimated using the Normalized Difference Vegetation Index (NDVI), which is a widely used measure in epidemiological studies investigating the relationship between greenness and health (Squillacioti et al., 2024; Gascon et al., 2016). The NDVI is a continuous variable that ranges from -1 to 1, with negative values indicating non-vegetated surfaces such as water bodies, snow, or sand, while zero NDVI values indicate barren or hard surfaces like rock, concrete, or areas with little to no vegetation, such as built environments. Conversely, positive NDVI values reflect the presence of vegetation, with higher positive values corresponding to denser and healthier vegetation.

In our study, the NDVI was derived from the Landsat 5 Thematic Mapper and Landsat 7 Enhanced Thematic Mapper Plus (ETM+) surface reflectance datasets with a spatial resolution of 30 x 30 m. Pixel selection was performed using Google Earth Engine, excluding negative values (e. g., water or snow) and pixels affected by clouds or cloud shadows. To best capture vegetation coverage, we used only satellite imagery from



† Some participants have more than one characteristic

Fig. 1. Flowchart of study population.

^{*} Some participants have missing data for more than one outcome

[†] Some participants have more than one characteristic

^{*} Some participants have missing data for more than one outcome.

the greenest season (May to August). However, as satellite images are captured every 16 days, cloud cover during this limited period can lead to substantial missing data, especially in northern regions. Given the relatively stable inter-annual variation in NDVI (Kazmierski et al., 2011; Das and Sarkar, 2023), the ATHLETE project (https://athleteproject.eu/) adopted a more robust estimation method to improve accuracy and reduce missing data. NDVI was calculated within circular buffers of 100, 300, and 500 m around each participant's geocoded residential address applying a 5-year NDVI average, incorporating the year of each pregnancy trimester and the four preceding years. Exposure during pregnancy was estimated by assigning a 5-year moving average to each trimester based on its start year. Lastly, trimester-specific values were averaged to obtain an overall NDVI exposure estimate for the full pregnancy.

The World Health Organization (WHO) does not provide recommendations specific to an exact NDVI buffer size for epidemiological studies. However, it recommends that, in Europe, residents should have access to urban green spaces of at least 0.5–1 ha within 300 m of their homes, which roughly corresponds to a 5-min walking distance (Urban green spaces: a brief for action, 2017). Research also supports using an NDVI buffer of at least a 300-m, as it more effectively captures the variability in surrounding greenness compared to smaller buffers, notably in urban settings (Gascon et al., 2016). Based on this, we selected the 300-m NDVI buffer as the measure of greenness for our main analyses.

2.3. Outcomes

Children's respiratory health and allergies at the 6- and 12-year follow-ups were assessed using parent-completed questionnaires adapted for the Pélagie cohort. They are based on the French version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires (Asher et al., 1995), which have been validated for the French population and are widely used for epidemiological studies on childhood asthma and allergies (Charpin et al., 1998). Our study focused on three primary outcomes: ever asthma, ever rhinitis, and ever eczema. Using these three outcomes, we also created a multimorbidity phenotype with three categories: no disease, one disease, and ≥2 diseases.

We defined ever asthma based on a parent-declared doctor-diagnosis of asthma. At the 6-year follow-up, it was determined through positive answers to both of the next questions: "Has your child ever had asthma attacks since birth?" and if yes: "Has your child's asthma been confirmed by a doctor?". At the 12-year follow-up, it was established through a positive response to the question "Has your child ever been diagnosed with asthma by a physician?".

Ever rhinitis, both at 6- and 12-year follow-up, was determined through a positive answer to the next question: "Since birth, has your child ever had sneezing, a runny nose or a blocked nose, even though they had no respiratory infection (no cold, nor rhinopharyngitis, nor flu ...)?".

We defined ever eczema based on a parent-declared doctor-diagnosis of eczema. At the 6-year follow-up, it was determined through positive answers to both of the next questions: "Since birth, has your child ever suffered from eczema or atopic dermatitis?" and If yes: "Has your child's eczema been confirmed by a doctor?". At the 12-year follow-up, it was established through a positive response to the question "Since your child was born, has a physician ever told you they had eczema?".

2.4. Covariates

Potential confounders of the relationship between exposure to residential greenness during pregnancy and childhood asthma, rhinitis, and eczema were identified from the existing literature. The covariates selected for adjustment included the child's sex and age, the mother's age and education level at inclusion, and the mother's smoking habits and the area-level socioeconomic status during pregnancy. $PM_{2.5}$ concentrations during pregnancy and the season at the start of pregnancy

were considered for supplementary analyses.

Self-reported data on maternal characteristics was collected through the inclusion questionnaire. Smoking habits during pregnancy were classified into three categories: non-smokers and former smokers, smokers at the start of pregnancy but that quit before inclusion, and smokers at inclusion. Mother's education level at inclusion was categorized into three classes: less than high school, high school diploma, and graduate education. The season at the start of pregnancy was ascertained based on the start date of pregnancy declared by the doctor in the maternity chart. Information about the child's sex was obtained from the maternity and pediatric charts completed at birth by healthcare personnel.

Area-level socioeconomic status was estimated using the 2009 French Deprivation Index (FDep09). This index defines social disadvantage as an accumulation of material and social disadvantages at the IRIS (aggregated units for statistical information) level, which divides the French territory into "neighborhoods" with a population of around 2000 (Rey et al., 2009). FDep was calculated in terciles (1st tercile (low deprived), 2nd tercile (medium deprived), and 3rd tercile (high deprived)) for the French general population at each IRIS. Each participant was assigned a deprivation level based on the IRIS of the residential address where they spent the most time during pregnancy.

Degree of urbanization during pregnancy was calculated using the GHSL SMOD Settlement model, which classifies $1~\rm km^2$ grid cells according to three main spatial entities: Urban Centre, Urban Cluster, and Rural Grid Cells (Florczyk et al., 2019). For our analysis, we created a binary variable to partition study participants into rural (Rural Grid Cells) and urban areas (Urban Centre and Urban Cluster Grid Cells) on the basis of their residential address, i.e., where they spent the most time during pregnancy.

Exposures to outdoor $PM_{2.5}$ during pregnancy were also estimated at each participant residential address. Annual mean $PM_{2.5}$ levels were estimated using a Land Use Regression (LUR) model developed for the ELAPSE project http://www.elapseproject.eu/, which incorporated satellite data, chemical transport models, and land use variables (de Hoogh et al., 2018). The model was applied to $100 \times 100 m$ grids across Western Europe. To estimate exposure during pregnancy, spatial estimates for the year 2010 were temporally adjusted (back-extrapolated) following ESCAPE guidelines (de Hoogh et al., 2013), using NO₂ data from a single background monitoring station (station FR19006, Rennes ENSP). The back-extrapolated daily averages were aggregated to a 9-month average corresponding to each pregnancy. More details on the estimation of air pollution during pregnancy for the Pélagie cohort can be found in a previous publication (Patlán-Hernández et al., 2024).

2.5. Statistical analyses

We decided to conduct complete case analyses, as the amount of missing data was minimal, with less than $2\,\%$ missing for each variable and less than $3\,\%$ across all variables at each follow-up. Therefore, only participants with no missing data for outcome variables, greenness exposure, and adjustment covariates were included.

Population characteristics including their exposure to surrounding residential greenness were described using frequencies, percentages, means, standard deviations, quartiles, and interquartile ranges (IQR). Differences between participants with and without asthma, rhinitis, or eczema were assessed using Chi-square tests for categorical variables, Wilcoxon Rank Sum tests for continuous variables that did not meet the assumption of normality, and Student's t-tests for those that followed a normal distribution. Comparisons between multimorbidity phenotype categories, using the no-disease category as reference, were conducted using One-Way ANOVA for continuous variables and Chi-square tests for categorical variables.

The associations of the NDVI within 300m with each of the three primary outcomes were separately analyzed using binary logistic regression models. To investigate the associations between the NDVI

within 300m and the multimorbidity phenotype categories, we used multinomial logistic regression models using the no-disease category as reference. Results were reported as odds ratios (OR) with 95 % confidence intervals (95 % CI) for a 0.1-unit increase of NDVI. All models were performed with an increasing order of adjustment: univariate analyses, *model 1:* adjusted by child's sex and age, mother's age at inclusion, and smoking habits during pregnancy, *model 2:* adjustment model 1+ maternal education level at inclusion, and *model 3:* adjustment model 2+ area-level socioeconomic status. To evaluate the linearity of the relationship between the NDVI within 300m and each health outcome, we performed models with restricted cubic splines (df = 4) and compared them to our main linear models using a likelihood ratio test for nested models.

We also performed interaction tests between the NDVI and the degree of urbanization to evaluate potential effect modification. As type and distribution of green spaces vary from urban to rural settings, additional analyses were performed stratifying by participants' degree of urbanization during pregnancy to account for the potential modification effect of degree of urbanization. Additional analyses with the NDVI within 300m categorized in terciles were carried out to further assess linearity of the associations between the NDVI within 300m during pregnancy and childhood asthma, rhinitis, eczema, and their multimorbidity.

To confirm the robustness of our findings, we carried out different sensitivity analyses. We performed models with additional adjustment for $PM_{2.5}$ exposure, average of daily mean temperature, and average of daily mean relative humidity during pregnancy to account for potential residual confounding from these variables. Also, as the NDVI was calculated using only the data from the greenest months, we performed analyses further adjusting for the season at the start of pregnancy to account for possible measurement error. We also performed analyses using the NDVI within 100 and 500 m buffers. Finally, given the high prevalence of our outcomes, which could lead to an overestimation of relative risks when using logistic regression, we performed additional analyses using Poisson regression models with robust error variance, and log-binomial regression models to verify the robustness of our main findings (Callas et al., 1998).

All statistical analyses were performed using R software (R 4.2.2).

3. Results

3.1. Demographic characteristics of the participants

The baseline characteristics between respondents and non-respondents at the 6- and 12-year follow-ups among all singleton live births included in the cohort (n = 3322) are compared in Table S1. Respondent mothers tended to be older, had a higher educational attainment, and were less likely to smoke during pregnancy, this last suggesting healthier prenatal behaviors among respondent families. Additionally, respondents had lower exposure to air pollutants and higher NDVI values during pregnancy, and were more likely to reside in rural areas.

Among the 1325 children included in the 6-year follow-up analyses, 50 % were boys, and the mean age was 6.2 (± 0.2) years (Table 1). Mother's mean age at inclusion was 30.5 years, 77.1 % of mothers did not smoke during the pregnancy, 69 % of them had a graduate education, 50.4 % had low socio-economic deprivation and 64.3 % of them lived in a rural setting during pregnancy. The 1119 mother-child pairs included in the 12-year follow-up analyses presented very similar characteristics (Table 1).

Prevalence of asthma, rhinitis, and eczema at the 6-year follow-up were 11.9~%, 19.5~% and 22.3~% respectively, and 11.6~% of children suffered from at least two of these diseases. At the 12-year follow-up, prevalence of asthma, rhinitis, and eczema were of 10.1~%, 23.2~% and 18.9~% respectively, and 11.3~% of children had at least two diseases (Table 1). Additionally, both at 6 and 12 years, children with asthma

Table 1Baseline characteristics of participants included for 6-year and 12-year follow-up analyses.

up analyses.		
	6-year follow-up (n = 1325)	12-year follow-up (n = 1119)
Sex, n (%)		
Boys	663 (50.0)	562 (50.2)
Girls	662 (50.0)	557 (49.8)
Age in years, mean (SD)	6.20 (0.20)	12.61 (0.34)
Mother's age in years at	30.54 (3.99)	30.68 (3.98)
inclusion, mean (SD)		,
Mother tobacco smoking during p	regnancy, n (%)	
	1022 (77.1)	882 (78.8)
Smoker at the start of pregnancy	171 (12.9)	141 (12.6)
who has quit	, ,	
Smoker at inclusion	132 (10.0)	96 (8.6)
Maternal education level at inclu-		
Under high school	188 (14.2)	122 (10.9)
High school diploma	223 (16.8)	186 (16.6)
Graduate education	914 (69.0)	811 (72.5)
French Deprivation Index (FDep)		
1st tercile (low deprived)	667 (50.4)	590 (52.7)
2nd tercile (medium deprived)	414 (31.2)	343 (30.7)
3rd tercile (high deprived)	244 (18.4)	186 (16.6)
Season at the start of pregnancy,		
Spring	323 (24.4)	287 (25.6)
Summer	345 (26.0)	300 (26.8)
Autumn	317 (23.9)	261 (23.3)
Winter	340 (25.7)	271 (24.2)
Degree of urbanization during pro		_, _ (,
Urban	473 (35.7)	411 (36.7)
Rural	852 (64.3)	708 (63.3)
NDVI, median (IQR)		
100m buffer	0.51 (0.13)	0.51 (0.13)
300m buffer	0.54 (0.12)	0.54 (0.12)
500m buffer	0.55 (0.11)	0.55 (0.12)
Air pollutants concentration (µg/		
PM _{2.5}	15.15 (3.32)	15.28 (3.53)
Department of residence at inclus		
22 - Côtes-d'Armor	350 (26.4)	286 (25.6)
29 - Finistère	75 (5.7)	59 (5.3)
35 - Ille-et-Vilaine	861 (65.0)	753 (67.3)
56 - Morbihan	39 (2.9)	21 (1.9)
Prevalence of outcomes	(=)	()
Ever asthma, n (%)	158 (11.9)	113 (10.1)
Ever rhinitis, n (%)	259 (19.5)	260 (23.2)
Ever eczema, n (%)	296 (22.3)	212 (18.9)
Multimorbidity phenotype		, ,
No disease, n (%)	812 (61.3)	701 (62.6)
1 disease, <i>n</i> (%)	359 (27.1)	291 (26.0)
≥ 2 diseases, n (%)	154 (11.6)	127 (11.3)
Ever asthma $+$ ever rhinitis, n	33 (2.5)	33 (2.9)
(%)		
Ever asthma $+$ ever eczema, n (%)	24 (1.8)	10 (0.9)
Ever rhinitis + ever eczema, <i>n</i> (%)	51 (3.8)	44 (3.9)
Ever asthma + ever rhinitis + ever eczema, <i>n</i> (%)	46 (3.5)	40 (3.6)
	11 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	

NDVI 100m, 300m, and 500m: Normalized Difference Vegetation Index at 100-, 300-, and 500-m circular buffer around residential address; $PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm ; SD: standard deviation; IQR: interquartile range.

showed a significantly higher prevalence of rhinitis and eczema compared to children without asthma (table S2 and table S3). The same tendency was observed among children suffering either rhinitis or eczema, suggesting a strong correlation between the 3 conditions. Furthermore, we observed that the coexistence of rhinitis and eczema was the most common combination both at 6- and 12-year follow-up (Table 1). No significant differences in the prevalence of outcomes were observed between urban and rural areas at either follow-up, except for asthma at 12 years which was significantly higher in urban areas (p=0.05) (Table S4).

Baseline characteristics of participants according to their status of

asthma, rhinitis, and eczema at 6- and 12-year follow-ups are respectively presented in table S2 and table S3. At 6 years old, participants with asthma or eczema compared to participants without the disease were more likely to be boys (58.2 % vs 48.9 % and 56.8 % vs 48.1 %, respectively). Furthermore, the mean age of mothers of children with asthma or rhinitis was significantly lower compared to mothers of children without the disease (29.9 vs 30.6 years and 29.8 vs 30.7 years, respectively). No other significant differences according to children's disease status were observed among the rest of covariates. At the 12-year follow-up, participants with asthma or rhinitis compared to participants without the disease were more likely to be boys (64.6 % vs 48.6 % and 60.8 % vs 47 %, respectively). Mothers of children with eczema had higher education compared to mothers of children without the disease (79.7 % vs 70.8 %). Compared to mothers of children without asthma, a higher proportion of mothers of children with asthma resided in urban areas (45.1 % vs 35.8 %) and were exposed to higher levels of PM_{2.5} (median value 16.1 vs 15.2 μg/m³). Lastly, a significantly higher proportion mothers of children with rhinitis started their pregnancies during spring or summer (30.4 % vs 24.2 % and 28.1 % vs 26.4 % respectively). Otherwise, no other significant differences among covariates according to children's disease status were observed. Similar trends were observed for the baseline characteristics of participants according to each multimorbidity profile (Table S5).

At baseline, mothers from urban areas consistently exhibited lower levels of socioeconomic deprivation (p < 0.01) and higher educational attainment (p < 0.0001) compared to their rural counterparts (Table S4). Also, mothers from urban areas were exposed to significantly higher air pollution levels (p < 0.0001) and lower NDVI values across all buffer sizes (p < 0.0001).

3.2. Surrounding residential greenness during pregnancy

The median residential NDVI within 300m exposure during pregnancy was 0.57 (IQR = 0.09). Median NDVI values during pregnancy remain consistent across buffer sizes for participants either at 6-or 12-years of follow-up (Table S6). Rural participants show higher NDVI exposure than urban participants (median NDVI within a 300m buffer 0.57 vs 0.45), and this result is also similar for the other NDVI buffers (Table S7). The standard deviations across buffer sizes are relatively small, indicating limited variance in vegetation exposure among participants. A statistically significant but weak negative correlation was observed between all NDVI buffers and outdoor $PM_{2.5}$ concentrations during pregnancy ($r \leq -0.43$). Pearson's correlation coefficients for all NDVI buffer sizes and $PM_{2.5}$ are shown in Figs. S2 and S3.

3.3. Association of surrounding residential greenness during pregnancy with childhood asthma, rhinitis, eczema, and their multimorbidity

Fully-adjusted analyses carried out with participants from the 6-year follow-up did not show evidence of associations between 0.1 increase in NDVI within 300m during pregnancy and asthma (OR = 0.94, 95 % CI = 0.79–1.13, p=0.47), or rhinitis (0.99 (0.86–1.15), p=0.92). However, we observed a protective association with eczema (0.87 (0.76–1.00), p=0.05) (Table 2). For 12-year follow-up participants, fully-adjusted analyses did not show evidence of associations of NDVI within 300m during pregnancy with asthma (0.88 (0.72–1.07), p=0.20), rhinitis (1.06, (0.92–1.23), p=0.43), nor eczema (0.96, (0.82–1.12), p=0.61) (Table 2). For the multimorbidity phenotype, at 6 years, a statistically significant protective association between the NDVI within 300m and the single-disease category was observed (0.87, (0.76–0.99), p=0.03) but no other statistically significant associations were found at either follow-up. Results of other levels of adjustment for all outcomes were similar to those from the fully adjusted models (Table S8).

Both at 6- and 12-year follow-up, no interactions between the degree of urbanization and the NDVI within 300m were found for any outcome (Table S9). For participants at the 6-year follow-up, stratified analyses

Table 2Adjusted associations of surrounding residential greenness during pregnancy (NDVI 300m) with ever asthma, ever rhinitis, ever eczema, and the multimorbidity phenotype among children at 6- and 12-years of follow-up.

Disease	6-year follow-up (n $= 1325$)			12-year follow-up (n $=$ 1119)		
	OR	95 % CI	p- value	OR	95 % CI	p- value
Ever asthma	0.94	[0.79–1.13]	0.52	0.88	[0.72–1.07]	0.20
Ever rhinitis	0.99	[0.86-1.15]	0.89	1.06	[0.92-1.23]	0.43
Ever eczema	0.87	[0.76-1.00]	0.05	0.96	[0.82-1.12]	0.61
Multimorbidity	phenoty	pe				
No disease	Ref.	•		Ref.		
1 disease	0.87	[0.76-0.99]	0.03	1.05	[0.91-1.21]	0.53
>2	0.92	[0.76–1.11]	0.37	0.94	[0.77–1.14]	0.52
diseases		-				

NDVI 300m: Normalized Difference Vegetation Index at 300 m circular buffer around residential address; OR: Odds Ratio; CI: confidence interval. OR (95 % CI) were calculated for an increase of 0.1-unit in NDVI. All models were adjusted for child's sex and age, mother's age and education level at birth, mother's tobacco smoking habits during pregnancy and area-level socioeconomic status during pregnancy (French Deprivation Index).

by degree of urbanization during pregnancy showed no statistically significant results for asthma, nor for rhinitis. Conversely, a marginally statistically significant protective association was observed for eczema in urban areas $(0.80 \ (0.64-1.01), p=0.06)$. However, no association was found in rural areas (Table 3), suggesting that the effect observed in the main analyses is primarily driven by urban participants. In contrast to eczema, the results for the multimorbidity phenotype suggest that the effect observed in the main analyses for the single-disease category was predominantly influenced by rural participants. A statistically significant association was identified in this group $(0.77 \ (0.61-0.97), p=0.03)$ but not among urban participants. For children with two or more diseases, no associations were observed either in urban or rural areas. At the 12-year follow-up, no statistically significant results were observed for any outcome when stratifying by degree of urbanization.

Table 3Adjusted associations of surrounding residential greenness during pregnancy (NDVI 300m) in urban versus rural areas with ever asthma, ever rhinitis, ever eczema, and the multimorbidity phenotype at 6- and 12-years of follow-up.

Disease	Urban area			Rural area		
	OR	95 % CI	p- value	OR	95 % CI	p- value
6-year follow-u	ір					
Ever asthma	0.89	[0.67-1.21]	0.45	1.03	[0.75-1.41]	0.87
Ever rhinitis	1.06	[0.82-1.40]	0.66	0.84	[0.65-1.08]	0.18
Ever eczema	0.80	[0.64-1.01]	0.06	0.97	[0.76-1.25]	0.82
Multimorbidity	phenoty	р е				
No disease	Ref.			Ref.		
1 disease	0.84	[0.67-1.05]	0.12	0.77	[0.61-0.97]	0.03
\geq 2	0.88	[0.64-1.22]	0.44	1.00	[0.72-1.38]	0.98
diseases						
12-year follow	v-up					
Ever asthma	0.92	[0.68-1.27]	0.62	0.98	[0.66-1.46]	0.92
Ever rhinitis	0.99	[0.77-1.28]	0.95	1.18	[0.90-1.54]	0.23
Ever eczema	0.83	[0.64-1.08]	0.17	0.97	[0.73-1.28]	0.81
Multimorbidity	phenoty	<i>т</i> ре				
No disease	Ref.	_		Ref.		
1 disease	0.99	[0.77-1.27]	0.92	1.01	[0.78-1.31]	0.92
\geq 2	0.86	[0.63-1.18]	0.36	1.08	[0.74-1.57]	0.69
diseases						

NDVI 300m: Normalized Difference Vegetation Index at 300 m circular buffer around residential address; OR: Odds Ratio; CI: confidence interval. OR (95 % CI) were calculated for an increase of 0.1-unit in NDVI. All models were adjusted for child's sex and age, mother's age and education level at birth, mother's tobacco smoking habits during pregnancy and area-level socioeconomic status during pregnancy (French Deprivation Index).

3.4. Supplementary analyses

Despite observing no differences between our main models and models with restricted cubic splines (Figs. S4–S5), we further explored the possible non-linear effects by categorizing the NDVI within 300m in terciles. These analyses did not show associations of the NDVI within 300 m exposure during pregnancy with asthma, rhinitis, nor eczema at either follow-up and all of the p-for-trend values were \geq 0.15 (Table S10).

Sensitivity analyses with further adjustment for $PM_{2.5}$, and for the season at the start of pregnancy yielded similar results as those from the main model (Table S11). Models with further adjustment on the average of daily mean temperature, and the average of daily mean relative humidity during pregnancy also yielded similar results to those from the main model (data not shown). Similarly, analyses using the NDVI within the 100 and 500 m buffers showed consistent results with those from analyses using the 300 m buffer (Table S12). Finally, results from analyses using Poisson regression models with robust error variance, and log-binomial regression models, were consistent with those from the main analyses using logistic regression models (Table S13). The protective effect of the NDVI on eczema and the single-disease category of the multimorbidity phenotype remained statistically significant in all sensitivity analyses.

4. Discussion

Despite the fact that most of our results showed no associations of surrounding residential greenness during pregnancy and the studied outcomes, we observed some protective effects for eczema and the single-disease category of the multimorbidity phenotype at the 6-year follow-up. Overall, stratified analyses by the degree of urbanization showed similar tendencies and effect sizes even if results were non-statistically significant.

Our study provides new insights by focusing on the effects of surrounding greenness during pregnancy, particularly in a predominantly rural population, which is an underrepresented group in epidemiological studies and where health impacts may differ from urban settings due to variations in vegetation. To our knowledge, only eight studies using the NDVI as greenness measure have examined its associations during pregnancy on childhood asthma (Kuiper et al., 2020; Stanescu et al., 2024; Fernandes et al., 2024; Sbihi et al., 2015; Shiroshita et al., 2024; Rantala et al., 2024; Mansouri et al., 2024; Abellan et al., 2024), and four of them have shown non-significant results (Kuiper et al., 2020; Fernandes et al., 2024; Shiroshita et al., 2024; Abellan et al., 2024). Similarly, our analysis for asthma, both at 6- and 12-year follow-up, showed no significant associations with the NDVI within 300m during pregnancy. We did not find any associations between the NDVI within 300m during pregnancy and rhinitis, which is in line with the literature as among the four studies using the NDVI as greenness measure (Kuiper et al., 2020; Yang et al., 2024; Lin et al., 2022; Paciência et al., 2023), three of them reported non-significant results (Kuiper et al., 2020; Lin et al., 2022; Paciência et al., 2023). Literature regarding the effects of surrounding residential greenness during pregnancy on childhood eczema is even more limited than for asthma and rhinitis. We identified only one study using the NDVI as measure of exposure to examine this relationship (Lin et al., 2022). In this study, Lin et al. found that prenatal exposure to the NDVI within 250m was not associated with eczema at the age of 2 years, but higher odds were observed in association with the NDVI within 500m (1.28 (1.04-1.59)). These results are difficult to compare with ours, since in this study eczema was assessed at 2 years. In our study, we found that the NDVI within 300m showed a protective effect on eczema at 6-years of follow-up but no significant results were observed at the 12-year follow-up. Given the paucity and heterogeneity of results regarding the effects of prenatal exposure to NDVI on eczema, it is difficult to conclude whether there is an effect or not, and further studies are needed.

Regarding the multimorbidity phenotype, we found a statistically significant protective association of the NDVI within 300m with the single-disease category at 6-year follow-up. This result suggests that it could be interesting to study the specific category of participants who have only one of the diseases as these individuals may have differences in susceptibility to exposure to green spaces or different underlying pathophysiological mechanisms compared to children with two or more of the diseases. All other results for the multimorbidity phenotype were non-statistically significant. The only similar study we identified is the one by Lin et al., which examined the effects of the NDVI on the occurrence of any of the considered allergic diseases in their study (eczema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, food allergy, and asthma), and found no associations for the NDVI within 250m but deleterious effects within 500m (Lin et al., 2022). Nevertheless, the results of Lin et al. are difficult to compare with ours as their outcomes were not the same and they do not specifically consider the diseases multimorbidity. To our knowledge, our study is the first to investigate the associations of surrounding residential greenness during pregnancy with asthma, rhinitis, and eczema multimorbidity in children, offering new perspectives on how early-life environmental exposures may contribute to multiple interconnected respiratory and allergic

Our study population represents a particularly novel population compared to those previously studied in the literature investigating the prenatal effects of the NDVI on childhood respiratory health and allergies. This is the first study to be carried out in France and in a predominantly rural population. One of our hypothesis was that as green spaces vary between urban and rural areas in terms of type, use, size, accessibility, and composition (Jarvis et al., 2020; Hartig et al., 2020; García de Jalón et al., 2021), their effects on childhood respiratory health and allergies could be different depending on the degree of urbanization. However, we did not find different results according to urbanicity strata. Only the single-disease category at the 6-years follow-up showed statistically significant decreased odds in association with the NDVI within 300m during pregnancy in rural areas (0.77 (0.61-0.97), p=0.03), while in urban areas no effect was observed (0.84)(0.67-1.05), p=0.12). Moreover, confidence intervals overlapped between both strata in all results. We identified only two studies accounting for the urbanicity when studying the effects of greenness exposure during pregnancy. One focused on childhood asthma, showed deleterious effects in metropolitan areas but no associations in non-metropolitan areas (Shiroshita et al., 2024). The other examined the effects of prenatal greenness on childhood rhinitis and allergic rhinitis adjusting for urbanicity, and found a protective effect on rhinitis, but a deleterious effect on allergic rhinitis (Yang et al., 2024). This emphasizes the need for further research taking rural populations more prominently into account.

We acknowledge several limitations and strengths of our study. As described in a previous publication (Warembourg et al., 2024), a selection of the Pélagie cohort has been observed at baseline towards more highly-educated women with higher socioeconomic level than the general French population, which was slightly accentuated in subsequent follow-ups. This is also observed in our analysis population and may limit the generalization of our results. Moreover, our sample size may limit statistical power, which is even more limited in our stratified analyses and could partly explain the observed null associations. Furthermore, since pulmonary function measures and biomarkers were not available for our study population, we relied on parent-reported outcomes through self-administered questionnaires. For asthma and eczema, definitions are based on the parent-declared doctor-diagnosis. This reliance on self-reported data introduces the possibility of outcome misclassification, as participants may inaccurately report diagnoses due to recall bias or misunderstandings of their child's condition. Among our population, this misclassification would likely be non-differential, meaning it is not related to the exposure status, which could bias our results towards the null. Additionally, it is difficult to establish a clear

diagnosis of asthma in children under 6 years of age (Yang et al., 2019; Global Strategy for Asthma Management, 2023), which may lead to misclassification of asthma cases at the 6-year follow-up, explaining the lower prevalence of asthma observed at the 12-year follow-up as well as the difference in our observed results. Nevertheless, the questionnaires used were based on the French-validated version of the ISAAC questionnaire, which is widely recognized for its reliability in epidemiological studies and has been validated in multiple locations, ensuring a high level of accuracy in the assessment of childhood asthma and allergic diseases prevalence (García-Marcos et al., 2022; Gough et al., 2015).

In this study, NDVI was calculated using 5-year moving averages to provide more consistent and reliable estimates of exposure by reducing the impact of intermittent missing data due to cloud cover. This method, applied consistently across all ATHLETE cohorts, accounts for variability in image availability and reduces noise due to single-time-point anomalies. However, we acknowledge that this approach, along with the use of data from the greenest season, constitute another limitation as it may not accurately reflect the exposure during the pregnancy period. Yet, results of our analyses were robust after further adjustment for the season at the start of pregnancy. Also, associations were similar after adjustment for PM_{2.5}, except for the protective association with the single-disease category at 6 years where the result became nonsignificant. To explore small differences in the influence of spatial scale of the NDVI, we performed analyses using the NDVI within 100m and 500m circular buffers. The results from these analyses were consistent with those obtained using the 300m buffer, which was expected as the NDVI values across the three buffer sizes are highly correlated (Figs. S2 and S3), likely due to the limited spatial variability within small buffers (Gascon et al., 2016; Helbich, 2019). Two similar studies assessing the effects of NDVI during pregnancy on childhood asthma found no associations, which were consistent across the same three buffer sizes we used in our study (Rantala et al., 2024; Abellan et al., 2024). Moreover, the NDVI within 100m and 500m is also commonly used in epidemiological studies, therefore, our analysis using these buffer sizes enhance the comparability of our findings across research. For example, Yang et al. used only the 500m and 1000m buffers to assess the associations between NDVI during pregnancy and rhinitis in children aged 3-6 years. Our results for the NDVI within 500m show no significant association with rhinitis at 6 years, whereas their study indicated a protective effect. However, their results for the 1000m buffer were not significant (Yang et al., 2024). Furthermore, since logistic regression can overestimate relative risks when outcomes are not rare (Callas et al., 1998), as is the case in our study, we performed sensitivity analyses using Poisson regression models with robust error variance and log-binomial regression models to test the robustness of our estimates. The results from these alternative models were consistent with those obtained from the main logistic regression analyses, allowing us to validate the robustness of our findings.

In our study, we assessed surrounding residential greenness during pregnancy using the NDVI, which is the most widely used metric of greenness in epidemiological studies, allowing the comparability of our results with some of the existing evidence (Squillacioti et al., 2024; Gascon et al., 2016). Strengths of the NDVI lie in its accessibility, ease of use, and strong correlation with expert ratings of neighborhood greenness, as demonstrated in studies from Seattle and Barcelona (Gascon et al., 2016; Rhew et al., 2011). However, its limitations in capturing fine-scale variability (e.g., $30m \times 30m$ spatial resolution), notably for retrospective data older than a decade, and its sensitivity to contextual factors, such as vegetation density, temporal changes, and vegetation type or biodiversity highlight the need for complementary approaches when assessing the effects of greenness on health (Helbich, 2019; Sadeh et al., 2021; Klompmaker et al., 2018). For instance, land use mapping, which provides information on the functional aspects of green areas by differentiating between parks, forests, and other land uses, allows for a more nuanced understanding of how green spaces characteristics impact health (Gascon et al., 2016; Dennis et al., 2018; Zaldo-Aubanell et al.,

2021). In dense urban areas, alternative metrics like Linear Spectral Unmixing have shown greater precision by disaggregating the relative contributions of different land covers and reducing misclassification (Sadeh et al., 2021). Similarly, indices like the Green View Index and the Natural Space Index offer unique advantages by focusing on visible green spaces or incorporating factors such as accessibility and quality, which the NDVI alone cannot fully address (Rugel et al., 2017; Larkin and Hystad, 2019). These alternatives highlight the importance of customized green space metrics specific to different environmental contexts and research questions. Beyond these objective metrics, subjective indicators of green space, such as perceived accessibility, safety, and aesthetic quality, provide valuable insights into how people perceive and interact with these environments (Gianfredi et al., 2021; Nguyen et al., 2021; Teeuwen et al., 2024). These measures capture dimensions which also influence the relationship between green spaces and health outcomes, providing a more comprehensive approach to assess the effects of green spaces on health and a more holistic understanding of these effects (Rugel et al., 2017; Mears et al., 2019). For example, areas with comparable NDVI scores may yield different effects on health depending on residents' perceptions and experiences, emphasizing the need to integrate both objective and subjective data. Therefore, future research must not only refine exposure assessments through the use of high-resolution satellite imagery and dynamic longitudinal data, but also integrate diverse indicators such as biodiversity, canopy coverage, and subjective measures of green space. Furthermore, metrics and definitions of green spaces across studies should be harmonized to ensure comparability across studies.

The mechanisms underlying the impact of green spaces during pregnancy on fetal and child health remain unclear. However, it has been proposed that mechanisms similar to those associated with postnatal exposure could be involved. These include stress reduction, promotion of social interactions, community cohesion and physical activity, mitigation of environmental hazards such as air pollution, noise, and heat, and enhanced exposure to diverse environmental microbiota (Dadvand et al., 2019; Buchholz et al., 2023). In urban environments, industrial and traffic-related air pollution are major contributors to sensitization and the worsening of allergic conditions later in life as it increases responsiveness to allergens (D'Amato et al., 2015; Bosch-Cano et al., 2011; Sedghy et al., 2018). Therefore, pathways related to the air pollution mitigation have received the most attention (Dadvand et al., 2019). For instance, some studies have found that increased greenness was associated with lower exposure to particulate air pollution and with reduced traffic-related pollution in schools (Dadvand et al., 2019), and reduced levels of serum IgE specific to inhalant allergens in children, which is a biomarker of asthma and allergic rhinitis (Ruokolainen et al., 2015). On the other hand, green spaces could also have deleterious effects on respiratory health and allergies through increased exposure to allergens like pollen and fungal spores, or chemicals such as pesticides (Dadvand et al., 2019). Early-life exposure to these environmental factors can induce sensitization through mechanisms involving Th2-mediated immune responses, characterized by cytokines such as IL-4, IL-5, and IL-13, which stimulate IgE production and promote eosinophilic inflammation (Brandt et al., 2015; Deng et al., 2016; Chen et al., 2021). Sensitization is particularly critical during early childhood when the immune system is still developing and exhibits heightened plasticity, predisposing individuals to allergic diseases such as allergic asthma, which is the most frequent asthma phenotype (Burbank et al., 2017; Huang et al., 2021). This variety of allergens highlights the complexity of the mechanisms by which green spaces impact respiratory health and allergies (Dadvand et al., 2019). Furthermore, effects of green spaces may be influenced by other factors such as the existing biodiversity in green spaces, differences in vegetation allergenicity, seasonal variations, and regional or climatic conditions (Dadvand et al., 2019). For example, in addition to proximity to natural areas, the biodiversity within these spaces has shown to contribute to richer microbiota in children, potentially lowering the risk of developing

allergies by improving immune regulation (Dadvand et al., 2019; Buchholz et al., 2023). Additionally, research has shown contrasting effects of green spaces on respiratory health in Mediterranean versus Euro-Siberian climates, highlighting once more the need for context-specific green space assessments to better understand these complex relationships (Dadvand et al., 2019). All these mechanisms are more complex when we consider the effects of green spaces during prenatal exposure. However, to the best of our knowledge, there are no studies on this subject.

5. Conclusion

Overall, our study did not find associations between surrounding residential greenness during pregnancy and the considered childhood respiratory and allergic outcomes, though some protective effects were suggested for eczema and the single-disease category of the multimorbidity phenotype at 6 years. Substantial variability remains in results across studies, likely due to differences in population characteristics, greenness measures, and regional factors, with the degree of urbanization playing a significant role. Therefore, future research should more prominently consider rural populations, and incorporate more refined approaches to assess green space, combining both objective and subjective measures in order to better understand the complex mechanisms through which green spaces impact respiratory health and allergies.

CRediT authorship contribution statement

Alan R. Patlán-Hernández: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. Christine Monfort: Writing - review & editing, Investigation, Data curation. Etienne Audureau: Writing - review & editing, Funding acquisition. Marta Cirach: Writing - review & editing, Data curation. Ralph Epaud: Writing - review & editing, Funding acquisition. Kees de Hoogh: Writing - review & editing, Investigation, Data curation. Sophie Lanone: Writing - review & editing, Funding acquisition. Parisa Montazeri: Writing – review & editing, Data curation. Danielle Vienneau: Writing - review & editing, Investigation, Data curation. Charline Warembourg: Writing - review & editing, Investigation, Data curation. Cécile Chevrier: Writing - review & editing, Investigation. Marine Savouré: Writing - review & editing, Validation, Supervision, Methodology, Conceptualization. Bénédicte Jacquemin: Writing – review & editing, Validation, Supervision, Proj-Funding administration, Methodology, acquisition, Conceptualization.

Ethical statement

All participants gave informed consent and the French ethics committees approved the study procedures.

Data sharing

The PELAGIE cohort data comply with the European regulation on the protection of personal data (25/05/2018). This regulation is based on a logic of compliance and increased responsibility of the actors who access to the data. In addition, the cohort study complies with the French "informatique et liberté" law (law n°78-17, January 1978, 2018). Access to data is thus possible following the agreement of the cohort principal investigators (Cécile Chevrier, Charline Warembourg) and on condition that the actors demonstrate respect for these European and French principles of personal data protection, to strengthen the rights of individuals. Further enquiries can be directed to the corresponding author.

Funding

This work is part of the REMEDIA project funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 874753.

The PELAGIE cohort has been funded (since its inception) by Inserm, the French Ministries of Health (2003–2004), Labor (2002–2003), and Research (ATC 2003–2004), the French National Institute for Public Health Surveillance (InVS, 2002–2006), the National Agency for Research (ANR, 2005–2008, 2010–2012, 2015–2019), the French Agency for Environmental Health Safety (Afsset/ANSES, 2007–2009, 2009–2012, 2019–2023), the French Agency for Drug Safety (2013–2017), the Fondation de France (2014–2017, 2015–2018, 2017–2020, 2019–2021, 2021–2024, 2023–2026), the French Ministry of Ecology (PNRPE 2014–2016), the Research Institute of Public Health (IResP 2011–2014), and the following European programs: Hi-WATE (2007–2009), ENRIECO (2008–2010), and OBERON (2019–2023) and REMEDIA (2020–2024).

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.

Acknowledgments

This work is part of a thesis prepared in the framework of the Doctoral Network in Public Health coordinated by the EHESP. We are grateful to the physicians and nurses and all the families who participated in the study (and continue to do so). We especially thank Nathalie Costet, Véronique Villalon, and Isabelle Coiffec who contributed to the PELAGIE cohort in general.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121730.

Data availability

The authors do not have permission to share data.

References

- Abellan, A., Warembourg, C., Mensink-Bout, S.M., Ambros, A., de Castro, M., Fossati, S., et al., 2024. Urban environment during pregnancy and lung function, wheezing, and asthma in school-age children. The generation R study. Environ Pollut 344, 123345.
- Asher, M., Keil, U., Anderson, H., Beasley, R., Crane, J., Martinez, F., et al., 1995. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur. Respir. J. 8 (3), 483–491.
- Bosch-Cano, F., Bernard, N., Sudre, B., Gillet, F., Thibaudon, M., Richard, H., et al., 2011. Human exposure to allergenic pollens: a comparison between urban and rural areas. Environ. Res. 111 (5), 619–625.
- Brandt, E.B., Biagini Myers, J.M., Acciani, T.H., Ryan, P.H., Sivaprasad, U., Ruff, B., et al., 2015. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. J. Allergy Clin. Immunol. 136 (2), 295–303.e7.
- Buchholz, V., Bridgman, S., Nielsen, C., Gascon, M., Tun, H., Simons, E., et al., 2023. Natural green spaces, sensitization to allergens, and the role of Gut Microbiota during infancy. mSystems 8.
- Burbank, A.J., Sood, A.K., Kesic, M.J., Peden, D.B., Hernandez, M.L., 2017. Environmental determinants of allergy and asthma in early life. J. Allergy Clin. Immunol. 140 (1), 1–12.
- Callas, P.W., Pastides, H., Hosmer, D.W., 1998. Empirical comparisons of proportional hazards, poisson, and logistic regression modeling of occupational cohort data. Am. J. Ind. Med. 33 (1), 33–47.
- Cao, N.W., Zhou, H.Y., Du, Y.J., Li, X.B., Chu, X.J., Li, B.Z., 2023. The effect of greenness on allergic rhinitis outcomes in children and adolescents: a systematic review and meta-analysis. Sci. Total Environ. 859, 160244.

- Celebi, Sozener Z., Özbey Yücel, Ü., Altiner, S., Ozdel Oztürk, B., Cerci, P., Türk, M., et al., 2022. The external exposome and allergies: from the perspective of the epithelial barrier hypothesis. Front Allergy 3, 887672.
- Charpin, D, Kubler, MCK, Oryszczyn, MP, Ray, P, Raherison, C, Taytard, A, et al., 1998. Présentation générale de l'étude ISAAC. Rev Fr Allergol 38 (4), 275–282. https://doi.org/10.1016/S0335-7457(98)80041-5.
- Chen, J.C., Chan, C.C., Ting, N.C., Kuo, M.L., 2021. Allergen exposure in murine neonates promoted the development of asthmatic lungs. Biomedicines 9 (6), 688.
- 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 [Internet]. Springer International Publishing, Cham, pp. 121–130. https://doi.org/10.1007/978-3-030-02318-8 6.
- Das, S., Sarkar, S.K., 2023. Spatio-temporal variability of vegetation and its relation to different hydroclimatic factors in Bangladesh. Heliyon 9 (8), e18412.
- de Hoogh, K., Wang, M., Adam, M., Badaloni, C., Beelen, R., Birk, M., et al., 2013. Development of land use regression models for particle composition in twenty study areas in Europe. Environ. Sci. Technol. 47 (11), 5778–5786.
- de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., et al., 2018. Spatial PM2.5, NO2, O3 and BC models for Western Europe – evaluation of spatiotemporal stability. Environ. Int. 120, 81–92.
- Delmas, M.C., Guignon, N., Leynaert, B., Moisy, M., Marguet, C., Fuhrman, C., 2017.
 Augmentation de la prévalence de l'asthme chez le jeune enfant en France. Rev. Mal. Respir. 34 (5), 525–534.
- Deng, Q., Lu, C., Yu, Y., Li, Y., Sundell, J., Norbäck, D., 2016. Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children. Respir. Med. 121, 67–73.
- Dennis, M., Barlow, D., Cavan, G., Cook, P., Gilchrist, A., Handley, J., et al., 2018. Mapping urban green infrastructure: a novel landscape-based approach to incorporating land use and land cover in the mapping of human-dominated systems. Land 7 (1) 17
- D'Amato, G., Holgate, S.T., Pawankar, R., Ledford, D.K., Cecchi, L., Al-Ahmad, M., et al., 2015. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the world allergy organization. World Allergy Organ J [Internet] 8 (1). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L605165019&from=export.
- EUROCAT Special Report, 2012. Congenital anomalies are a major group of mainly rare diseases [Internet]. Newtownabbey, Northern Ireland: EUROCAT central registry. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/eurocat-pub-docs/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf.
- Fernandes, A., Avraam, D., Cadman, T., Dadvand, P., Guxens, M., Binter, A.C., et al., 2024. Green spaces and respiratory, cardiometabolic, and neurodevelopmental outcomes: an individual-participant data meta-analysis of >35.000 European children. Environ. Int. 190, 108853
- Florczyk, A.J., Corbane, C., Ehrlich, D., Freire, S., Kemper, T., Maffenini, L., et al., 2019. GHSL Data Package 2019: Public Release GHS P2019. Publications Office of the European Union. Luxembourg.
- García de Jalón, S., Chiabai, A., Quiroga, S., Suárez, C., Ščasný, M., Máca, V., et al., 2021.

 The influence of urban greenspaces on people's physical activity: a population-based study in Spain. Landsc Urban Plan 215, 104229.
- Garcia-Aymerich, J., Benet, M., Saeys, Y., Pinart, M., Basagaña, X., Smit, H.A., et al., 2015. Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. Allergy 70 (8), 973–984.
- García-Marcos, Luis, Innes Asher, M., Pearce, Neil, Ellwood, Eamon, Bissell, Karen, Chiang, Chen-Yuan, et al., 2022. The burden of asthma, hay fever and eczema in children in 25 countries: GAN Phase I study. Eur. Respir. J. 60 (3), 2102866.
- Gascon, M., Cirach, M., Martínez, D., Dadvand, P., Valentín, A., Plasència, A., et al., 2016. Normalized difference vegetation index (NDVI) as a marker of surrounding greenness in epidemiological studies: the case of Barcelona city. Urban For. Urban Green. 19, 88–94.
- Gianfredi, V., Buffoli, M., Rebecchi, A., Croci, R., Oradini-Alacreu, A., Stirparo, G., et al., 2021. Association between urban greenspace and health: a systematic review of literature. Int J Environ Res Public Health 18 (10), 5137.
- [Internet] Global Strategy for Asthma Management and Prevention, 2023. Global Initiative for Asthma. Available from: www.ginasthma.org.
- Gough, H., Grabenhenrich, L., Reich, A., Eckers, N., Nitsche, O., Schramm, D., et al., 2015. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr. Allergy Immunol. 26 (5), 431–437.
- Gunawardena, K.R., Wells, M.J., Kershaw, T., 2017. Utilising green and bluespace to mitigate urban heat island intensity. Sci. Total Environ. 584–585, 1040–1055.
- Gutvirtz, G., Wainstock, T., Sheiner, E., Pariente, G., 2022. Prematurity and long-term respiratory morbidity—what is the critical gestational age threshold? J. Clin. Med. 11 (3), 751.
- Hartig, T., Astell-Burt, T., Bergsten, Z., Amcoff, J., Mitchell, R., Feng, X., 2020. Associations between greenspace and mortality vary across contexts of community change: a longitudinal ecological study. J. Epidemiol. Community Health 74 (6), 534-540.
- Helbich, M., 2019. Spatiotemporal contextual uncertainties in green space exposure measures: exploring a time series of the normalized difference vegetation indices. Int J Environ Res Public Health 16 (5), 852.
- Hu, C.Y., Yang, X.J., Gui, S.Y., Ding, K., Huang, K., Fang, Y., et al., 2021. Residential greenness and birth outcomes: a systematic review and meta-analysis of observational studies. Environ. Res. 193, 110599.
- Huang, C.F., Chie, W.C., Wang, I.J., 2021. Effect of environmental exposures on allergen sensitization and the development of childhood allergic diseases: a large-scale population-based study. World Allergy Organ J 14 (1), 100495.

- Institute for Health Metrics and Evaluation. GBD compare. [cited 2022 Jan 21]. GBD Compare. Available from: https://vizhub.healthdata.org/gbd-compare/.
- Jarvis, I., Gergel, S., Koehoorn, M., van den Bosch, M., 2020. Greenspace access does not correspond to nature exposure: measures of urban natural space with implications for health research. Landsc Urban Plan 194, 103686.
- Kazmierski, M., Glémas, P., Rousseau, J., Tisseyre, B., 2011. Temporal stability of withinfield patterns of NDVI in non irrigated Mediterranean vineyards. OENO One 45 (2), 61
- Klompmaker, J.O., Hoek, G., Bloemsma, L.D., Gehring, U., Strak, M., Wijga, A.H., et al., 2018. Green space definition affects associations of green space with overweight and physical activity. Environ. Res. 160, 531–540.
- Kuiper, I.N., Markevych, I., Accordini, S., Bertelsen, R.J., Bråbäck, L., Christensen, J.H., et al., 2020. Associations of preconception exposure to air pollution and greenness with offspring asthma and hay fever. Int J Environ Res Public Health 17 (16), 5828.
- Larkin, A., Hystad, P., 2019. Evaluating street view exposure measures of visible green space for health research. J. Expo. Sci. Environ. Epidemiol. 29 (4), 447–456.
- Lin, L., Chen, Y., Wei, J., Wu, S., Wu, S., Jing, J., et al., 2022. The associations between residential greenness and allergic diseases in Chinese toddlers: a birth cohort study. Environ. Res. 214, 114003.
- Lovasi, G.S., O'Neil-Dunne, J.P.M., Lu, J.W.T., Sheehan, D., Perzanowski, M.S., Macfaden, S.W., et al., 2013. Urban tree canopy and asthma, wheeze, rhinitis, and allergic sensitization to tree pollen in a New York city birth cohort. Environ. Health Perspect. 121 (4), 494–500.
- Mansouri, R., Lavigne, E., Talarico, R., Smargiassi, A., Rodriguez-Villamizar, L.A., Villeneuve, P.J., 2024. Residential surrounding greenness and the incidence of childhood asthma: findings from a population-based cohort in Ontario, Canada. Environ. Res. 249, 118316.
- Maritano, S., Moirano, G., Popovic, M., D'Errico, A., Rusconi, F., Maule, M., et al., 2022.
 Maternal pesticides exposure in pregnancy and the risk of wheezing in infancy: a prospective cohort study. Environ. Int. 163, 107229.
- 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.
- Mears, M., Brindley, P., Jorgensen, A., Ersoy, E., Maheswaran, R., 2019. Greenspace spatial characteristics and human health in an urban environment: an epidemiological study using landscape metrics in Sheffield, UK. Ecol. Indic. 106, 105464.
- Momas, I, Bougas, N, Rancière, F, Roda, C, Citerne, A, Viola, M, 2022. Impact de l'exposition à la pollution atmosphérique d'origine automobile sur la morbidité respiratoire et allergique au cours de l'enfance: leçons de la cohorte Paris. Bull Enidémiol Hebd. 23, 410–419.
- 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. Investig. 129 (4), 1504–1515.
- Nguyen, P.Y., Astell-Burt, T., Rahimi-Ardabili, H., Feng, X., 2021. Green space quality and health: a systematic review. Int J Environ Res Public Health [Internet] 18 (21). Available from: https://www.embase.com/search/results?subaction=viewrecord &id=1.2014165206&from=export.
- Paciência, I., Rantala, A.K., Antikainen, H., Hugg, T.T., Jaakkola, M.S., Jaakkola, J.J.K., 2023. Varying effects of greenness in the spring and summer on the development of allergic rhinitis up to 27 years of age: the Espoo Cohort Study. Allergy 78 (6), 1680–1682.
- Patlán-Hernández, A.R., Savouré, M., Audureau, E., Monfort, C., de Castro, M., Epaud, R., et al., 2024. Associations of exposure to outdoor PM2.5 and NO2 during pregnancy with childhood asthma, rhinitis, and eczema in a predominantly rural French mother-child cohort. Environ Pollut 363, 125206.
- Pawankar, R., 2014. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J 7, 12.
- Rantala, A.K., Paciência, I., Antikainen, H., Hjort, J., Hugg, T.T., Jaakkola, M.S., et al., 2024. Residential greenness during pregnancy and early life and development of asthma up to 27 years of age: the Espoo Cohort Study. Environ. Res. 252, 118776.
- Rey, G., Jougla, E., Fouillet, A., Hémon, D., 2009. Ecological association between a deprivation index and mortality in France over the period 1997 – 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health 9 (1), 33.
- Rhew, I.C., Vander Stoep, A., Kearney, A., Smith, N.L., Dunbar, M.D., 2011. Validation of the normalized difference vegetation index as a measure of neighborhood greenness. Ann. Epidemiol. 21 (12), 946–952.
- 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 populationlevel health research. Environ. Res. 159, 474–483.
- Ruokolainen, L., Von Hertzen, L., Fyhrquist, N., Laatikainen, T., Lehtomäki, J., Auvinen, P., et al., 2015. Green areas around homes reduce atopic sensitization in children. Allergy Eur J Allergy Clin Immunol 70 (2), 195–202.
- Sadeh, M., Brauer, M., Dankner, R., Fulman, N., Chudnovsky, A., 2021. Remote sensing metrics to assess exposure to residential greenness in epidemiological studies: a population case study from the Eastern Mediterranean. Environ. Int. 146, 106270.
- Sasso, F., Izard, M., Beneteau, T., Rakotozandry, T., Ramadour, M., Annesi-Maesano, I., et al., 2019. 18-year evolution of asthma and allergic diseases in French urban schoolchildren in relation to indoor air pollutant levels. Respir. Med. 148, 31–36.
- 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 (9), 1131–1133.
- Sedghy, F., Varasteh, A.R., Sankian, M., Moghadam, M., 2018. Interaction between air pollutants and pollen grains: the role on the rising trend in allergy. Rep Biochem Mol

- Shin, Y.H., Hwang, J., Kwon, R., Lee, S.W., Kim, M.S., et al., GBD 2019 Allergic Disorders Collaborators, 2023. Global, regional, and national burden of allergic disorders and their risk factors in 204 countries and territories, from 1990 to 2019: a systematic analysis for the global burden of disease study 2019. Allergy 78 (8), 2232–2254.
- Shiroshita, A., Kataoka, Y., Wang, Q., Kajita, N., Anan, K., Yajima, N., 2024. Pollen as a mediator between environmental greenness during pregnancy and infancy periods and childhood persistent asthma: a nationwide retrospective birth cohort study in Japan. Environ Pollut 363, 125039.
- Sigurdardottir, S.T., Jonasson, K., Clausen, M., Lilja Bjornsdottir, K., Sigurdardottir, S.E., Roberts, G., et al., 2021. Prevalence and early-life risk factors of school-age allergic multimorbidity: the EuroPrevall-iFAAM birth cohort. Allergy 76 (9), 2855–2865.
- Soriano, J.B., Kendrick, P.J., Paulson, K.R., Gupta, V., Abrams, E.M., Adedoyin, R.A., et al., 2020. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet Respir. Med. 8 (6), 585–596.
- Squillacioti, G., Fasola, S., Ghelli, F., Colombi, N., Pandolfo, A., La Grutta, S., et al., 2024. Different greenness exposure in Europe and respiratory outcomes in youths. A systematic review and meta-analysis. Environ. Res. 247, 118166.
- Stanescu, C., Talarico, R., Weichenthal, S., Villeneuve, P.J., Smargiassi, A., Stieb, D.M., et al., 2024. Early life exposure to pollens and increased risks of childhood asthma: a prospective cohort study in Ontario children. Eur. Respir. J. 63 (4), 2301568.
- Taylor, L., Hochuli, D.F., 2017. Defining greenspace: multiple uses across multiple disciplines. Landsc Urban Plan 158, 25–38.
- Teeuwen, R., Milias, V., Bozzon, A., Psyllidis, A., 2024. How Well do NDVI and OpenStreetMap Data Capture People's Visual Perceptions of Urban Greenspace? Landsc Urban Plan, vol. 245, 105009.

- The Global Asthma Report 2022, 2022. Int J Tuberc Lung Dis 26 (1), 1-104.
- 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. University of East Anglia, Room 1.23 Queen's Building, Norwich Research Park, Norwich, United Kingdom, pp. 628–637, 166((Twohig-Bennett C., cbennett10@qub.ac.uk; Jones A.) Norwich Medical School.
- Urban green spaces: a brief for action, 2017. World Health Organization. Regional Office for Europe, Copenhagen, Denmark.
- Wang, X., Zhou, N., Zhi, Y., 2023. Association between exposure to greenness and atopic march in children and adults—A systematic review and meta-analysis. Front. Public Health 10, 1097486.
- Warembourg, C., Monfort, C., Costet, N., Rouget, F., Pelé, F., Garlantézec, R., et al., 2024. Cohort Profile: the PELAGIE mother-child cohort. Int. J. Epidemiol. 53 (3), dyae064.
- Wong, N.H., Tan, C.L., Kolokotsa, D.D., Takebayashi, H., 2021. Greenery as a mitigation and adaptation strategy to urban heat. Nat. Rev. Earth Environ. 2 (3), 166–181.
- Yang, C.L., Gaffin, J.M., Radhakrishnan, D., 2019. Question 3: can we diagnose asthma in children under the age of 5 years? Paediatr. Respir. Rev. 29, 25–30.
- Yang, B.Y., Zhao, T., Hu, L.X., Browning, M.H.E.M., Heinrich, J., Dharmage, S.C., et al., 2021. Greenspace and human health: an umbrella review. Innovation 2 (4), 100164.
- Yang, L., Chen, H., Gao, H., Wang, Y., Chen, T., Svartengren, M., et al., 2024. Prenatal and postnatal early life exposure to greenness and particulate matter of different size fractions in relation to childhood rhinitis - a multi-center study in China. Sci. Total Environ. 938, 173402.
- Zaldo-Aubanell, Q., Serra, I., Sardanyés, J., Alsedà, L., Maneja, R., 2021. Reviewing the reliability of Land Use and Land Cover data in studies relating human health to the environment. Environ. Res. 194, 110578.