Full length article

Green spaces and respiratory, cardiometabolic, and neurodevelopmental outcomes: An individual-participant data meta-analysis of >35.000 European children

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ABSTRACT

Studies evaluating the benefits and risks of green spaces on children's health are scarce. The present study aimed to examine the associations between exposure to green spaces during pregnancy and early childhood with respiratory, cardiometabolic, and neurodevelopmental outcomes in school-age children. We performed an Individual-Participant Data (IPD) meta-analysis involving 35,000 children from ten European birth cohorts across eight countries. For each participant, we calculated residential Normalized Difference Vegetation Index (NDVI) within a 300 m buffer and the linear distance to green spaces (meters) during prenatal life and childhood. Multiple harmonized health outcomes were selected: asthma and wheezing, lung function, body mass index, diastolic and systolic blood pressure, non-verbal intelligence, internalizing and externalizing problems, and ADHD symptoms. We conducted a two-stage IPD meta-analysis and evaluated effect modification by socioeconomic status (SES) and sex. Between-study heterogeneity was assessed via random-effects meta-regression. Residential surrounding green spaces in childhood, not pregnancy, was associated with improved lung function, particularly higher FEV_1 ($\beta = 0.06$; 95 %CI: 0.03, 0.09 $I^2 = 4.03$ %, $p < 0.001$) and FVC ($\beta = 0.07$; 95 %CI: 0.04, 0.09 $I^2 = 0$ %, $p < 0.001$) with a stronger association observed in females ($p < 0.001$). This association remained robust after multiple testing correction and did not change notably after adjusting for ambient air pollution. Increased distance to green spaces showed an association with lower FVC ($\beta = -0.04$; 95 %CI: -0.07, -0.02, $I^2 = 4.8$, $p = 0.001$), with a stronger effect in children from higher SES backgrounds ($p < 0.001$). No consistent associations were found between green spaces and asthma, wheezing, cardiometabolic, or neurodevelopmental outcomes, with direction of effect varying across cohorts. Wheezing and neurodevelopmental outcomes showed high between-study heterogeneity, and the age at outcome assessment was only associated with heterogeneity in internalizing problems.. This large European meta-analysis suggests that childhood exposure to green spaces may lead to better lung function. Associations with other respiratory outcomes and selected cardiometabolic and neurodevelopmental outcomes remain inconclusive.

1. Introduction

Prenatal and childhood are considered critical periods for the development and maturation of organ structure and function (Gluckman et al., 2007). Early-life stressors related to the urban environment, such as air pollution and road traffic noise, alongside its social determinants, have been identified as risk factors for the onset of respiratory, cardiometabolic, and neurodevelopmental disorders across the life course (Gascon et al., 2016; Vrijheid, 2014). The natural environment, including vegetation surrounding residences (i.e., residential greenness) and accessibility to green spaces (i.e., walkable distance from home to parks, urban forest, etc), may mitigate those urban hazards to improve child growth and development.

Green spaces may benefit health by reducing the harmful effects of air pollution, noise, and heat, enhancing the development and maturation or diversity of the immune system and microbiome, promoting stress recovery, improving sleep and attention, and encouraging physical activity, play, and social cohesion (Markevych et al., 2017). Exposure to green spaces during pregnancy has been increasingly associated with improved birth outcomes (Toda et al., 2022; Yang et al., 2021), potentially leading to lasting effects on subsequent child health (Bijnens et al., 2020). Examining green space exposure separately during pregnancy and childhood is essential for identifying specific health effects and guiding targeted interventions across life stages.

Particularly in school-age children, recent longitudinal and cross-sectional studies found that living in areas with more vegetation and near green spaces was associated with better lung function (Almeida et al., 2022b; Fuertes et al., 2020). Cross-sectional studies have reported the benefits of green space exposures on maintaining normal blood pressure (Dzhambov et al., 2022; Warembourg et al., 2021) and a healthy weight status (Dadvand et al., 2014). Moreover, accumulating evidence suggests that exposure to green spaces during pregnancy and early childhood can positively affect neurodevelopment. This includes improved brain structure (Dadvand et al., 2018) and better performance on cognitive tests (Binter et al., 2022; Fernandes et al., 2023a), including intelligence (Almeida et al., 2022a; Bijnens et al., 2020), as well as

reduced risk of attention deficit hyperactivity disorder (ADHD) and other emotional problems (Amoly et al., 2014; Bijnens et al., 2020).

Despite the growing and promising studies in this field, the existing literature on the association between green spaces and health in childhood is still inconsistent for most outcomes (Cadman et al., 2022; Gascon et al., 2016; Luque-García et al., 2022; Zare Sakhvidi et al., 2023). Green spaces may have both positive and negative effects on different health outcomes; for instance, while they promote attention restoration, they may also expose children to allergens (Dadvand et al., 2014). For instance, studies examining the association of residential greenness and proximity to green spaces with diagnosed or parental-reported childhood asthma, have reported null, harmful, and beneficial effects (Dadvand et al., 2014; Fuertes et al., 2016; Parmes et al., 2020; Tischer et al., 2018; Yu et al., 2021). Moreover, potential adverse effects of green spaces, including the spread and higher concentrations of allergenic pollen, the concentration of disease vectors, and aspects related to crime and gentrification make it complex to disentangle their effects on health in specific contexts (Markevych et al., 2017; Zare Sakhvidi et al., 2023).

Part of these inconsistencies may be attributed to differing measurements of exposures and outcomes across studies within specific populations, often with a narrow focus on a single outcome or country (Labib et al., 2020; Yang et al., 2021; Zare Sakhvidi et al., 2023). Consequently, the number of studies examining both the risks and benefits of green spaces in relation to child health is restricted, with a reliance on limited outcomes from a single-site population (Dadvand et al., 2014). Additionally, a common challenge in systematic reviews within this field is the difficulty in aggregating data for meta-analysis, given the diversity in study design and measurement methods (Labib et al., 2020; Luque-García et al., 2022). Moreover, only a limited number of studies utilized individual participant data meta-analysis (IPD) (Fuertes et al., 2016; Parmes et al., 2020). Policymakers and practitioners may encounter challenges in comprehensively evaluating the impact of green spaces on child health due to conflicting and fragmented evidence (VanderWeele et al., 2020).

In this context, the present study aimed to examine the associations

between exposure to green spaces during pregnancy and early childhood with respiratory, cardiometabolic, and neurodevelopmental outcomes in school-age children. In this study, we focused on outcomes commonly evaluated in the literature, which have yielded inconsistent results in previous studies (Dadvand et al., 2014; Fuertes et al., 2016; Gascon et al., 2016; Luque-García et al., 2022). Additionally, the selection of these outcomes was guided by data availability across the cohorts. We conducted an IPD meta-analysis across 10 European birth cohorts, involving up to 35,000 children and assessing a comprehensive set of 12 harmonized health outcomes.

2. Material and methods

2.1. Study design and participating cohorts

This study was conducted within the EU Child Cohort Network (Jaddoe et al., 2020) as part of the European Union-funded LifeCycle, EUCAN-Connect, and ATHLETE projects. Data from each cohort were harmonized and accessed via a central analysis server. Details of how variables were harmonized are provided in the EU Child Cohort Network Variable Catalogue (https://data-catalogue.molgeniscloud.org) and elsewhere (Pinot de Moira et al., 2021).

Cohorts were eligible for inclusion in the present study if they had harmonized data on exposure to green space and any health outcome of interest measured in the age range from 3 to 12 years. The following 10 cohorts participated in the study: Amsterdam Born Children and their Development, the Netherlands (ABCD) (van Eijsden et al., 2011), Avon Longitudinal Study of Parents and Children, United Kingdom (ALSPAC) (Boyd et al., 2013; Fraser et al., 2013), Born in Bradford, United Kingdom (BiB) (Wright et al., 2013), Copenhagen subset of the Danish National Birth Cohort, Denmark (DNBC) (Olsen et al., 2001), Etude des Déterminants du développement et de la santé de l'Enfant, France (EDEN) (Heude et al., 2016), the Generation R Study, the Netherlands (GenR) (Kooijman et al., 2016), Infancia y Medio Ambiente, Spain, (INMA)(Guxens et al., 2012), Kaunas Birth Cohort, Lithuania (KANC) (Grazuleviciene et al., 2009), the Norwegian Mother, Father and Child Cohort Study, Norway (MoBa) (Magnus et al., 2016), Nascita e INFanzia: gli Effetti dell'Ambiente, Italy (NINFEA)(Richiardi et al., 2007).

Participants' consent was obtained by the source studies or home institutions from each cohort. Each participating cohort obtained ethical approval from its local ethics committee and consent from participants. The data from each cohort was analyzed remotely, and the lead author obtained consent (in the form of data access agreements) from each cohort study through the LifeCycle partners of the EU Child Cohort Network (Supplementary information Text S1).

2.2. Assessment of exposure to green space

As part of the LifeCycle project (Jaddoe et al., 2020), the assessment of green spaces followed a standardized protocol to ensure uniform collection of data across cohorts. Data on green spaces are available during pregnancy and specific time points in childhood. For the present study, we evaluated residential surrounding green space and residential distance to a major green space.

Residential surrounding green space was defined as the abstracted average Normalized Difference Vegetation Index (NDVI) within 100 m, 300 m, and 500 m buffers around the participant's residential address. NDVI is a widely used index to quantify vegetation by measuring the difference between near-infrared light (reflected by vegetation) and red light (absorbed by vegetation)("Landsat Normalized Difference Vegetation Index | U.S. Geological Survey," 2023). The values vary from −1 to 1, with higher values indicating more photosynthetic capacity and thus more vegetation. We used cloud-free images from Landsat 4–5 Thematic Mapper (TM) and Landsat 7 Enhanced Thematic Mapper Plus (ETM +) within 30x30m resolution to develop the NDVI maps. One or more images were selected for each cohort/city to cover the entire study

period (Supplementary Information, Table S1.1). We have selected images corresponding to the greenest period of the year (summer for northern cohorts, spring for southern cohorts). Water was not removed but negative values in the images have been reclassified to null values previously. For this study, NDVI within a 300 m buffer was used as the main exposure based on World Health Organisation (WHO) recommendations on residential green space availability(WHO, 2017) ().

Distance to green spaces was measured as the linear (Euclidean) distance in meters from the participant's residential address to the nearest major green space (i.e., >0.5 ha) (WHO, 2017) The Europe-wide "Urban Atlas" or local layers were used to extract maps of urban green spaces. One or two maps were selected for each cohort/city to cover the entire study period, and assigned to time points of interest (Supplementary Information, Table S1).

In this study, we selected exposure to green spaces at two specific time points: during pregnancy, utilizing the mother's home address, and during childhood, defined as the period from 3 to 12 years of age. For the childhood period, four cohorts (ALSPAC, DNBC, GENR, INMA) have complete residential histories from birth to age 12, allowing precise geocoding for each period of interest. However, in other cohorts, exact residential addresses were available only at specific ages (5, 7, 8, 10, and/or 11). In each cohort, we selected the most recent exposure time point preceding the years of outcome assessment. This approach aimed to address data availability variations across cohorts and the selection of satellite images as close in time as possible to the outcomes assessment period. Furthermore, only exposures during pregnancy were included for younger cohorts (BiB and KANC) due to data availability (Supplementary Information, Table S1.1).

2.3. Assessment of health outcomes

This study focused on child health outcomes, including respiratory, cardiometabolic, and neurodevelopmental factors, which have been related to an increased risk of common chronic diseases later in life and potentially influenced by residential green spaces (Gascon et al., 2016). To enhance the robustness of our meta-analysis, we specifically selected outcomes available in at least three cohorts. For each outcome with repeated measures, we selected the latest assessment between ages 3 to 12 for every child. Twelve harmonized outcomes were selected: ever asthma diagnosis at any point between 3 to 12 years of age (yes/no), current wheezing in the past 12 months (yes/no), FEV_1, FVC and FEV_1/FVC ratio as measures of lung function (spirometry), body mass index (BMI), diastolic and systolic blood pressure (mmHg), non-verbal intelligence, internalizing and externalizing problems, and ADHD symptoms test scores.

Respiratory outcomes on doctor diagnosis of ever asthma (yes/no) and current wheezing were assessed by most of the cohorts from parental reported questionnaires in Childhood (ISAAC)(Asher et al., 1995). Forced vital capacity (FVC) as a parameter of lung volume and size, and forced expiratory volume in the first second (FEV_1) and FEV_1/FVC ratio as parameters of airway obstruction were measured by spirometry according to the American Thoracic Society and European Respiratory Society guidelines(Quanjer et al., 2012). Lung function measures were converted to z-scores for age, height, sex, and ethnicity based on the Global Lung Initiative 2012 reference values(Quanjer et al., 2012).

We calculated BMI as weight (kg)/height (m) squared. We used WHO growth standard values to transform BMI into sex and age-specific z-scores(De Onis and Lobstein, 2010). Then, we excluded outliers that were more than ± 5 standard deviations from the sample mean. We evaluated the average systolic and diastolic peripheral blood pressure (mmHg) from multiple measures at the same assessment, utilizing raw data for our analysis (Warembourg et al., 2021).

Neurodevelopmental outcomes were assessed by validated neuropsychological tests. To ensure comparability of neurodevelopmental outcomes across cohorts, we used standardized scores per age within

each cohort for non-verbal intelligence. Higher scores denoted better performance (Essers et al., 2022; Nader et al., 2023). Additionally, for internalizing, externalizing, and ADHD scores, we applied square root operations to transform raw scores and achieve a normal distribution. Subsequently, we standardized the transformed values using z-score transformations within each cohort, where higher scores indicate more problems (Essers et al., 2022).

Additional details about each outcome assessment across cohorts can be found in the Supplementary Information, Tables S3, S4, and S5.

2.4. Covariates

A common minimal set of harmonized covariates relevant for respiratory, cardiometabolic, and neurodevelopmental outcomes and available in all the ten cohorts was selected (Supplementary Information, Table S2) including child age at outcome assessment (years) and sex (male/female) to avoid any residual confounding effect, maternal education at pregnancy (ISCED-2011/97 low/medium/high) as a proxy of individual-level socioeconomic status (SES), and area-level deprivation index (low deprivation = 1, medium deprivation = 2, high deprivation = 3) at pregnancy, smoking during pregnancy (yes/no), parity (null\multiparity) as a proxy of the presence of siblings and previous associations with childhood risk factors (Dadvand et al., 2014a; Gaillard et al., 2014), maternal age (years), and pre-pregnancy BMI (kg/m^2) of the mother – for those values ≤ 15 or ≥ 50 were considered outliers and then excluded. Furthermore, adjustments were applied to the neurodevelopmental outcomes as needed, including evaluator (examiner, parent, teacher or computerized) to account for different instruments used in the same cohort.

For cohorts that included multiple sub-studies (i.e., EDEN, INMA, NINFEA) we further adjusted for sub-cohort (EDEN-Nancy, EDEN-Poitiers, INMA-Gipuzkoa, INMA-Sabadell INMA-Valencia, NINFEA-Turin, NINFEA-Roma, NINFEA-Florence). Furthermore, for cohorts with a substantial proportion of mothers from countries other than Europe (i.e., ABCD, BiB, and GenR), we further adjusted by the maternal ethnic background based on (a) the color of the mother (white, non-white) or (b) country of origin of parents (western, non-western or mixed), where western countries include European Union, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Switzerland, USA and Vatican City. Non-western countries include all other countries, while mixed refers to one parent from a Western country and one parent from a non-Western country (Vinther et al., 2023).

2.5. Statistical analysis

2.5.1. Main analysis

Data from each cohort were accessed via a central analysis server using the R-based platform DataSHIELD (https://www.datashield.org). DataSHIELD allows privacy-preserving federated data analysis without the need to transfer the data to the analyst (Gaye et al., 2014; Wilson et al., 2017). Analyses were restricted to singleton pregnancies resulting in a live-born child. The sample sizes for exposures, outcomes, and covariates, as well as their combinations within the models, were detailed in the descriptive tables and associated plots in the results section. The final sample sizes varied due to differences in data availability, and missing values were managed using a complete case approach.

We examined the associations between residential surrounding green spaces and residential distance to a major green space with each child health outcome separately. The effect estimates were calculated per one-interquartile range (1-IQR) increase of NDVI across 300 m buffer and linear distance in meters from the residential address to the nearest major green space. We used logistic regression models for asthma diagnosis and current wheezing and linear regression models for all other outcomes. Regression models were fitted separately for each

cohort and regression coefficients and standard errors were combined using random effects meta-analysis (Basagaña et al., 2018) by using the restricted maximum likelihood estimator method. Cohorts were assigned weights based on the narrowest confidence interval (inverse-variance weighting) under the random-effects model to attain pooled estimates. Bonferroni corrections were applied to take account of multiple comparisons (0.05 / 12 outcomes * 2 exposures* 2 periods of life = 0.001).

2.5.2. Stratified analysis

To explore potential disparities in access to green spaces and health outcomes across socioeconomic status, we stratified the main models by maternal education level (low and medium vs. high) and by residential area-level deprivation index (low deprivation vs. medium/high deprivation). Additionally, we evaluated the potential effect modification by sex of the child.

2.5.3. Sensitivity analysis

For all the outcomes, the following sensitivity analyses were conducted: (1) NDVI within 100 m, and 500 m buffers around the participant's residential address; (2) excluding each cohort in turn - "leave-one-out analysis" approach - to detect high influential studies that might notably affect the pooled effect or heterogeneity (Viechtbauer and Cheung, 2010) and (3) restricting our main analysis to children aged 6 years or older due to potential variations in risk factors linked to onset mechanisms and developmental stages that differ across age groups. Additionally, (4) in meta-analyses characterized by high between-study heterogeneity, we performed meta-regression to explore whether the age of outcome assessment exhibited an independent association with the observed between-study heterogeneity. We determined high heterogeneity based on when either the I^2 value of approximately 60 % with Cochran's Q test p-value was ≤ 0.05, or when the 95 % confidence interval for $\tau 2$ did not include zero. This latter estimator is less influenced by the number of studies and their precision (Harrer et al., 2021; Vinther et al., 2023). We performed a meta-regression only for meta-analysis including five or more cohorts(Geissbühler et al., 2021).

Furthermore, (5) child age and sex were not included as covariates for associations of green spaces with z-scores of lung function, BMI, and age-standardized non-verbal intelligence variables; and finally, (6) the associations between green spaces and any of the outcomes that survived multiple correction testing were further adjusted for estimates of outdoor exposure to NO_2 and $PM_{2.5}$ (annual average concentrations): at the home addresses during pregnancy and at the same year as the selected childhood green space exposure. These pollutants were selected because of the availability of data and to evaluate whether the effect of green spaces on health operates independently or partly through the influence of air pollution (Markevych et al., 2017). The methods for the exposure assessment and distribution of NO_2 and $PM_{2.5}$ in the selected cohorts are described in the Supplementary Information (Table S1 and S6, respectively).

Distributions of exposures, outcome measures, and covariates were presented for each cohort separately. In the descriptive analysis, neurodevelopmental outcomes were displayed as raw scores. However, direct comparisons between cohorts are not feasible due to variations in the instruments used across studies. Statistical analyses were performed using DataSHIELD through the Statistical Software R (v4.3). We used the dsBaseClient (v6.1.0) and ds.Helper (v1.0.3) DataSHIELD packages in combination with the dmetar R package (v.0.0.9) (Mathias et al., n.d.).

For consistency, for all aforementioned analyses, the statistical significance was considered at p ≤ 0.001 after multiple testing corrections.

3. Results

3.1. Study population

A range of 7452 (residential distance to green spaces and lung

function) up to 35,407 (NDVI and BMI) mother–child dyads in 10 cohort studies from eight countries had information on green space exposures, covariates, and at least one outcome of interest measured between 3 to 12 years of age (Fig. 1). The included cohorts varied in size from 1,999 children in EDEN to 13,836 in DNBC (Table 1). Descriptive information including characteristics of covariates and outcomes for study participants are displayed separately for each cohort in Tables 1 and 2. There were differences in the cohort-specific distributions of maternal education (range: 1.3 % to 43.3 % for mothers in the lowest educational group), maternal country of birth (range: 34.8 % to 92.5 % for Western countries); and level of area deprivation (range: 12.5 % to 85.1 % for children in the highest deprived areas).

3.2. Distribution of exposure to green spaces during pregnancy and childhood

Table 2 presents the distribution of the green space indicators. For residential surrounding green spaces, the mean and range of NDVI values in a 300-m buffer varied widely across cohorts. Overall, higher NDVI scores were observed during the childhood period compared to pregnancy. Also, cohorts from Northern Europe (i.e., KANC, and MoBa) were greener than those in Southern Europe (INMA and NINFEA). The NDVI values varied from a median of 0.23 (IQR = 0.10) in NINFEA (Italy) to 0.52 (IQR = 0.16) in MoBa (Norway) during the pregnancy period. During childhood, the values varied from a median of 0.26 (IQR = 0.11) in NINFEA (Italy) to 0.57 (IQR = 0.15) in MoBa (Norway). The median distance to green space (m) was similar in both periods and across cohorts, with a median range of 71.5 (IQR = 106) in EDEN (France) and 180.9 (IQR = 220.3) in ABCD (the Netherlands).

3.3. Health outcomes and associations with urban green spaces

The overall adjusted estimates per 1-IQR increase NDVI in a 300-meter buffer and 1-IQR increase in the residential distance in meters to a major green space during pregnancy and childhood with multiple

outcomes assessed during childhood (3–12 years) are displayed in Figs. 2a-c. Cohort-specific estimates are available in the Supplementary Information, Figures S1-S12.

3.3.1. Green spaces and respiratory outcomes

The prevalence of asthma diagnosis at school age ranged from 1.8 % in NINFEA to 14.4 % in ALSPAC, with a similar distribution for wheezing in the past 12 months (2.7 in NINFEA and 10.3 % in ALSPAC). Lung function measures varied across the four participating cohorts, with median scores ranging from −0.8 to 0.1 for FEV_1, −1.1 to 0.3 for FVC, and −0.3 to 1.3 for FEV1/FVC ratio GLI-z-scores. (Table 2).

Higher childhood exposure to residential surrounding green spaces was associated with higher lung function measures in school-age children, even after multiple testing correction. Specifically, we found that 1-IQR increase of NDVI in 300 m buffer was associated with higher FEV_1 z-scores (β = 0.06; 95 %CI: 0.03, 0.09 I^2 = 4.03 %, p=<0.001) and FVC z-scores scores (β = 0.07; 95 %CI: 0.04, 0.09 I^2 = 0 %, p=<0.001), respectively (Fig. 2a). In general, the heterogeneity between cohorts, as estimated by different parameters was low for these particular estimates.

Increased residential distance to green space during childhood period was associated with lower FEV_1 (β = −0.04; 95 %CI: −0.08, −0.01, I^2 = 28.1, p = 0.006) and FVC z-scores (β = −0.04; 95 %CI: −0.07, −0.02, I^2 = 4.8, p = 0.001) (Fig. 2a), with the latter association persisting following Bonferroni correction. Furthermore, there was a moderate to lower level of between-study heterogeneity observed for these estimates, as indicated by the I^2 statistics.

Regarding pregnancy exposures to green spaces, we did not observe any associations with lung function. Additionally, there were no clear and statistically significant associations observed of exposure to green spaces during the pregnancy and childhood periods with asthma and wheezing prevalence, as shown in Fig. 2a.

3.3.2. Green spaces and cardiometabolic outcomes

Regarding cardiometabolic outcomes, all ten cohorts had data on BMI z-scores, displaying differences across studies and ages. The mean
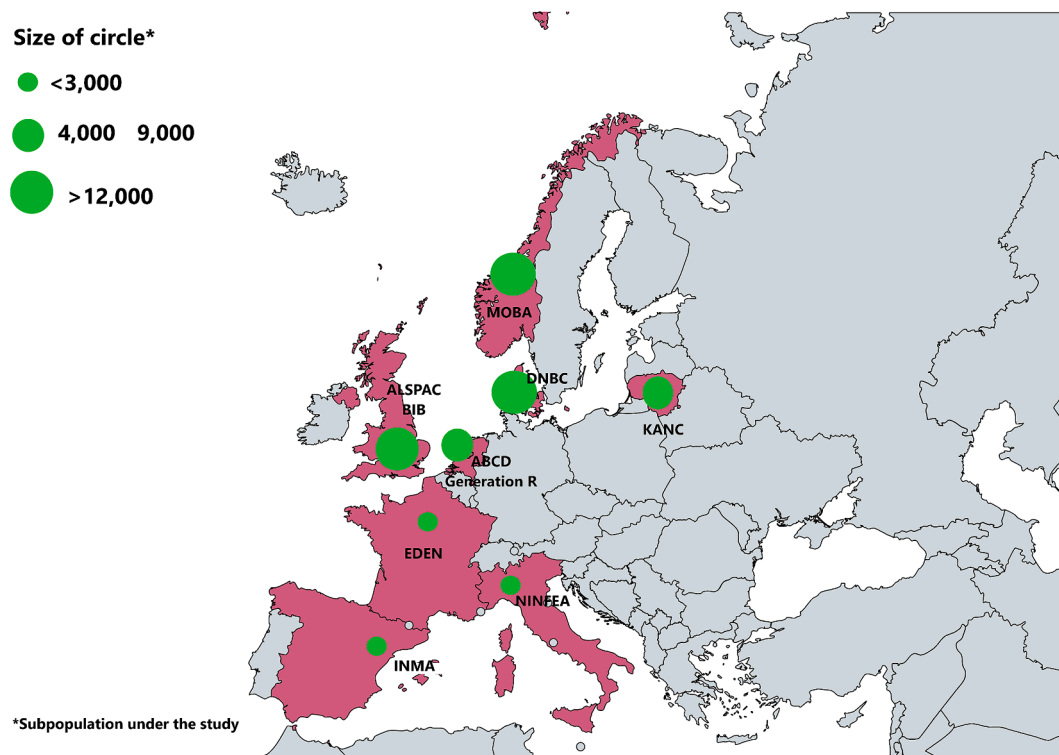

Fig. 1. Map of cohorts and number of participants involved in the present study. Figure. adapted from: https://lifecycle-project.eu/for-scientists/the-eu-child-cohort-network/

Table 1
Distribution of covariates at pregnancy per birth cohort.

Variables	ABCD (n = 7351)	ALSPAC (n = 13491)	BiB (n = 13183)	DNBC (n = 13836)	EDEN (n = 1999)	GenR (n = 9283)	INMA (n = 2084)	KANC (n = 4039)	MoBa (n = 12523)	NINFEA (n = 2744)
Child year of birth[1]	2004 (1)	1992 (1)	2009 (2)	2000 (2)	2004 (1)	2004 (2)	2005 (2)	2008 (1)	2007 (2)	2010 (5)
Pre-pregnancy BMI (kg/m^2)[2]	23.1 (3.9)	22.9 (3.8)	26.0 (5.6)	22.4 (3.4)	23.3 (4.6)	23.6 (4.4)	23.5 (4.3)	24.5 (4.6)	22.9 (3.5)	22. 2 (3.7)
Missing (n, %)	675 (9.2)	2842 (21.1)	8560 (65.0)	1297 (9.4)	118 (5.9)	2243 (24.2)	5 (0.2)	0 (0)	550 (4.4)	52 (1.9)
Maternal age[2]	31.2 (5.2)	26.7 (5.9)	27.5 (5.6)	30 (4.15)	29.5 (4.9)	30.4 (5.4)	31.8 (4.2)	28 (5.1)	31.3 (4.1)	33.6 (4.2)
Missing (n, %)	579 (7.9)	3300 (24.5)	0 (0)	1 (0.01)	95 (4.7)	1 (0.01)	154 (7.4)	0 (0)	9 (0.1)	127 (4.6)
Maternal smoking pregnancy[3]										
No	6570 (89.4)	7531 (55.8)	9086 (68.9)	9843 (71.1)	1398 (69.9)	5772 (62.2)	1342 (64.4)	3744 (92.7)	10,196 (81.4)	2484 (90.6)
Yes	772 (10.5)	3309 (24.5)	1786 (13.5)	3658 (26.4)	519 (26.0)	2079 (22.4)	648 (31.1)	294 (7.3)	2185 (17.5)	226 (8.2)
Missing (n, %)	9 (0.1)	2651 (19.6)	2311 (17.5)	342 (2.5)	82 (4.1)	1429 (15.4)	94 (4.5)	0 (0)	142 (1.13)	32 (1.2)
Parity[3]										
Multipara	3859 (52.5)	6548 (48.5)	7678 (58.2)	4916 (35.5)	1053 (52.7)	4013 (43.2)	936 (44.9)	2076 (51.4)	4331 (35.3)	653 (23.8)
Nullipara	3423 (46.6)	5341 (39.6)	5029 (38.1)	8927 (64.5)	847 (42.4)	4918 (53.0)	1141 (54.8)	1962 (48.6)	7931 (64.7)	1981 (72.2)
Missing (n, %)	69 (0.9)	1602 (11.8)	476 (3.6)	0 (0)	99 (4.9)	349 (3.7)	7 (0.3)	0 (0)	261 (2.1)	108 (4.0)
Sex of the child[3]										
Male	3704 (50.4)	6885 (51.0)	6799 (51.6)	6908 (49.9)	997 (49.9)	4692 (50.6)	1037 (49.8)	2073 (51.3)	6357 (50.8)	1319 (48.1)
Female	3647 (49.6)	6606 (49.0)	6384 (48.4)	6935 (50.1)	903 (45.2)	4588 (49.4)	979 (47.0)	1965 (48.7)	6166 (49.2)	1270 (46.3)
Missing (%)	0 (0)	0 (0.00)	0 (0)	0 (0)	99 (4.9)	0 (0)	68 (3.3)	0(0)	0 (0)	153 (5.6)
Maternal education[3]										
High	3626 (49.3)	1468 (10.9)	2768 (21.0)	8219 (59.4)	1021 (51.1)	3512 (37.8)	688 (33.0)	2149 (53.2)	9,558 (76.3)	1852 (67.5)
Medium	2023 (27.5)	7664 (56.8)	1561 (11.8)	1944 (14.0)	743 (37.2)	3738 (40.3)	845 (40.6)	523 (12.9)	1,788 (14.3)	757 (27.6)
Low	1637 (22.3)	2303 (17.1)	5709 (43.3)	1826 (13.2)	143 (7.1)	916 (9.8)	542 (26.0)	1366 (33.8)	162 (1.3)	117 (4.3)
Missing (n, %)	65 (0.9)	2056 (15.2)	3145 (23.8)	1854 (13.4)	92 (4.6)	1114 (12.0)	9 (0.4)	0 (0)	1,015 (8.1)	17 (0.6)
Maternal ethnic background[3]										
Western	3927 (53.4)	11,063 (82.0)	4592 (34.8)	–	1310 (79.8)	4766 (51.3)	1928 (92.5)	–	–	–
Non-Western	3362 (45.7)	2278 (1.7)	6078 (46.1)	–	91 (5.5)	3862 (41.6)	149 (7.1)	–	–	–
Mixed	–	0 (0)	212 (1.61)	–	–	0 (0)	0 (0.0)	–	–	–
Missing (n, %)	62 (0.8)	2200 (16.3)	2301 (17.4)	–	241 (14.7)	652 (7.0)	7 (0.4)	–	–	–
Area-level SES[3]										
Low deprived area	1412 (19.2)	3163 (23.4)	383 (2.9)	4799 (34.7)	706 (35.3)	1124 (12.1)	969 (46.5)	1084 (26.8)	2306 (18.4)	868 (31.7)
Medium deprived area	701 (9.5)	3855 (28.6)	1558 (11.8)	2175 (15.7)	457 (22.9)	1653 (17.8)	848 (40.7)	2036 (50.4)	4825 (38.5)	776 (28.3)
High deprived area	5052 (68.7)	4878 (36.2)	11,221 (85.1)	1844 (13.3)	691 (34.6)	5424 (58.4)	26 (12.5)	905 (22.4)	4633 (37.0)	633 (23.1)
Missing (n, %)	186 (2.5)	1595 (11.8)	21 (0.2)	5025 (36.3)	145 (7.2)	1079 (11.6)	6 (0.3)	13 (0.3)	759 (6.1)	465 (16.9)

[1] (n, median, IQR); [2] (n, mean, SD); [3] n (%).

(SD) ranged from −0.1 (1.3) in KANC to 0.7 (1.2) in INMA. As for systolic blood pressure, the mean (SD) ranged from 101.0 (8.5) in EDEN and 109.0 (10.5) mmHg in ALSPAC, while for diastolic blood pressure to 53.5 (8.4) in EDEN and 68.2 (10.9) mmHg in BiB (Table 2). There were no clear and statistically significant associations observed for green spaces and BMI z-scores or blood pressure. In general, all pooled estimates exhibited minimal between-study heterogeneity. (Fig. 2b).

3.3.3. Green spaces and neurodevelopmental outcomes

Five cohorts provided data on non-verbal intelligence measures, while seven cohorts included assessments on behavioral problems (Table 2). We did not find clear significant associations, with most

estimates close to null for both pregnancy and childhood periods, with larger confidence intervals for non-verbal intelligence estimates. There was considerable between-study heterogeneity observed across these outcomes, especially concerning the estimates for NDVI in both periods (>60 %) (Fig. 2c).

3.4. Stratified analysis

The associations between exposure to green spaces and multiple outcomes across maternal education level, strata of area-level deprivation, and child sex are presented in the Supplementary Information, Tables S7-15. Overall, when considering the corrected p-value for

Table 2

Distribution of selected outcomes[a] and green spaces exposures with respective age of assessment.

Variables	ABCD	ALSPAC	BiB	DNBC	EDEN	GenR	INMA	KANC	MoBa	NINFEA
Respiratory health										
Ever asthma[3]										
Yes	–	1946 (14.4)	501 (3.8)	1088 (7.9)	163 (8.1)	491 (5.3)	90 (4.3)		390 (3.1)	50 (1.8)
No	–	6815 (50.5)	10,895 (82.6)	8363 (60.4)	590 (62.3)	4924 (53.3)	1286 (61.7)		8167 (65.2)	1429 (52.1)
Mean age (SD)	–	8.0 (0.2)	6.4 (1.6)	10 (1.9)	5.9 (1.4)	8.7 (1.2)	7.9 (0.9)		4.6 (0.8)	8.5 (1.5)
Current wheezing[3]										
Yes	–	1390 (10.3)	–	596 (4.3)	165 (8.2)	309 (5.4)	178 (8.5)		–	75 (2.7)
No		9409 (69.7)	–	8866 (64.1)	1247 (29.4)	5392 (58.1)	1403 (67.3)			1417 (51.7)
Mean age (SD)		10.9 (1.9)		10 (1.9)	5.9 (1.4)	8.5 (1.5)	7.4 (1.6)		–	7.8 (2.1)
FEV$_1$ z-score[1]	–	3194, −0.04 (1.3)	–	–	894, −0.8 (1.3)	5096, 0.1 (1.2)	1581, 0.1 (1.3)		–	–
FVC Z-Score[1]		3194, −0.07 (1.3)			894, −1.1 (−2.2)	5096, 0.2 (1.8)	1581, 0.3 (1.3)			
FEV1 FVC ratio, z-score[1]		3194, 0.05 (1.4)			894, 1.3 (1.4)	5096, −0.1 (1.9)	1581, −0.3 (1.4)			
Mean age (SD)		8.5 (0.24)	–		5.0 (0.2)	9.1 (0.4)	7.4 (1.3)			
Cardiometabolic[2]										
BMI z-scores (SD)	5137, 0.1 (1.1)	9794, 0.4 (1.2)	10666, 0.4 (1.3)	9462, 0.01 (1.3)	1495, 0.0 (1.1)	7848, 0.4 (1.2)	1583, 0.7 (1.2)	559, −0.1 (1.1)	8037, 0.01 (1.1)	2033, 0.1 (1.2)
Mean age (SD)	8.5 (2.8)	11.1 (1.7)	6.8 (1.9)	9.9 (1.9)	8.0 (3.1)	7.8 (2.2)	8.6 (2.3)	3.7 (0.8)	7.0 (1.5)	6.7 (2.3)
DBP (mmHg)	–	4253, 57.1 (7.5)	8930, 68.2 (10.9)	–	1363, 53.5 (8.4)	6844, 60.0 (6.5)	1487, 61.5 (9.1)	–	–	–
Mean age (SD)		11.0 (1.9)	8.6 (1.5)		4.7 (0.8)	8.4 (1.4)	7.7 (1.4)			
SBP (mmHg)	–	4253, 109.0 (10.5)	8930, 108.6 (12.6)	–	1362, 101.0 (8.5)	6844, 104.0 (7.9)	1487, 105.0 (9.8)	–	–	–
Mean age (SD)		11.0 (1.9)	8.6 (1.5)		4.7 (0.8)	8.4 (1.4)	7.7 (1.4)			
Neurodevelopment (raw scores)[1]										
Non-verbal intelligence	1725, 16 (9)	7132, 99 (24)	–	–	1462, 94 (35)	5907, 31 (3)	1479, 31 (7)	–	–	–
Mean age (SD)	11.1 (0.3)	8.5 (0.9)			5.2 (0.1)	6.2 (0.5)	8.5 (2.0)			
Int. problems	3962, 1 (2)	9235, 2 (3)	2487, 3 (4)	9457, 2 (4)	1429, 3 (4)	6182, 4 (6)	1287, 4 (5)	–		–
Mean age (SD)	8.6 (3.1)	10.3 (2.3)	4.0 (0.2)	10 (1.9)	6.8 (1.8)	8.5 (1.9)	10.1 (1.0)			
Ext. problems	2843, 1 (1)	9395, 4 (4)	2487, 6 (5)	9455, 2 (3)	1428, 5 (6)	6296, 3 (6)	1287, 4 (6)			–
ADHD	2845, 0 (1)	9742, 3 (3)	–	9454, 2 (3)	1428, 3 (4)	4326, 5 (8)	1490, 5 (9)	–		1122, 5 (3)
Mean age (SD)	8.4 (3.1)	10.3 (2.2)	–	10 (1.9)	6.8 (1.8)	8.1 (0.2)	9.9 (1.9)	–		4.5 (1.8)
Exposures (pregnancy)[1]										
NDVI 300 m	**0.30 (0.12)**	**0.41 (0.10)**	**0.43 (0.17)**	**0.30 (0.12)**	**0.49 (0.2)**	**0.38 (0.14)**	**0.24 (0.2)**	**0.49 (0.1)**	**0.52 (0.16)**	**0.23 (0.10)**
Missing (n, %)	3209 (23.2)	1595 (11.8)	20 (0.2)	3208 (23.2)	117 (5.8)	1076 (11.6)	6 (0.29)	1 (0.02)	1861 (14.9)	388 (14.1)
Linear distance to green space, m (>5.000 m²) from home	**209.31 (255.56)**	**162.0 (213.16)**	**169.51 (217.45)**	**215.82 (242.4)**	**88.5 (144.0)**	**165.02 (185.8)**	**121.0 (161.9)**	**131.7 (181.7)**	**202.05 (351.44)**	**163.50 (181.15)**
Missing (n, %)	177 (2.4)	1901 (14.1)	21 (0.2)	3208 (23.2)	576 (28.8)	1082 (11.7)	37 (1.8)	1 (0.02)	1861 (14.9)	188 (14.1)
Exposure's childhood[1] (3–12 years old)										
NDVI 300 m	**0.43 (0.16)**	**0.49 (0.13)**	–	**0.33 (0.16)**	**0.50 (0.2)**	**0.44 (0.13)**	**0.27 (0.2)**	–	**0.57 (0.15)**	**0.26 (0.11)**
Missing (n, %)	1305 (17.7)	1560 (11.6)	–	8976 (64.9)	456 (22.8)	284 (3.1)	110 (5.3)	–	4843 (38.7)	1036 (37.8)
Linear distance to green space (>5.000 m2) from home	**180.9 (220.3)**	**154.07 (201.8)**	–	**232.0 (269.8)**	**71.5 (106.0)**	**152.9 (175.4)**	**112.0 (151.5)**	–	**148.97 (171.15)**	**158.1 (184.5)**
Missing (n, %)	1709 (23.2)	2008 (14.8)	–	8976 (64.9)	872 (43.6)	422 (4.5)	142 (6.8)	–	4843 (38.7)	1036 (37.8)
Age of exposure assessment (year)	5	8	–	7	5	8	6	–	5	4

[1] (n, median, IQR); [2] (n, mean, SD); [3] n (%); [a] One outcome (the latest available measure) at one time point selected within 3 to 12 years old. FEV$_1$ forced expiratory volume in the first second; FVC, Forced vital capacity; DBP, diastolic blood pressure; SBP, systolic blood pressure. For Non-Verbal Intelligence tests: the higher the score, the better the performance in the test; For ADHD, Internalization, and Externalization scales: higher scores indicated more behavioral problems. These measures cannot be directly compared between cohorts. BiB and KANC have only pregnancy exposures assigned. For more information on outcomes distribution see Supplementary Information, Table S3, S4, and S5.

Exposure	Sample	Asthma	OR	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	28821		1.02	(0.97,1.08)	0.474	0.00	2.84	0.90
NDVI_childhood	21668		1.02	(0.96,1.08)	0.524	0.00	3.90	0.69
Linear distance_pregnancy	28287		1.01	(0.95,1.07)	0.796	12.46	6.80	0.45
Linear distance_childhood	20977		0.97	(0.92,1.03)	0.316	0.00	1.74	0.94

Ever Asthma: yes/no
0.8 1 1.2

Exposure	Sample	Wheezing	OR	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	19887		0.99	(0.90,1.09)	0.877	26.49	5.83	0.32
NDVI_childhood	16448		0.93	(0.78,1.12)	0.451	73.85	16.58	0.01 △
Linear distance_pregnancy	19326		0.97	(0.91,1.04)	0.361	0.00	0.64	0.99
Linear distance_childhood	15715		0.97	(0.91,1.05)	0.464	3.59	3.13	0.68

Current Wheezing: yes/no
0.8 1 1.2

Exposure	Sample	Lung function (FEV1)	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	7994		0.02	(-0.02,0.06)	0.255	20.69	3.64	0.30
NDVI_childhood	7908		0.06	(0.03,0.09)	0.000	4.03	1.78	0.62
Linear distance_pregnancy	7679		-0.02	(-0.06,0.03)	0.423	53.79	6.44	0.09
Linear distance_childhood	7488		-0.04	(-0.08,-0.01)	0.006	28.10	4.13	0.25

Forced expiratory volume 1 second (GLI-zscore)
-0.1 0 0.1

Exposure	Sample	Lung function (FVC)	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	7958		0.01	(-0.02,0.04)	0.406	0.00	2.40	0.49
NDVI_childhood	7872		0.07	(0.04,0.09)	0.000	0.00	1.37	0.71
Linear distance_pregnancy	7643		-0.02	(-0.06,0.03)	0.471	52.34	6.22	0.10
Linear distance_childhood	7452		-0.04	(-0.07,-0.02)	0.001	4.88	2.46	0.48

Forced vital capacity(GLI-zscore)
-0.1 0 0.1

Exposure	Sample	Lung function (FEV1/FVC)	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	7958		0.00	(-0.03,0.03)	0.969	0.15	2.98	0.39
NDVI_childhood	7872		-0.02	(-0.05,0.01)	0.260	0.26	3.02	0.39
Linear distance_pregnancy	7643		0.00	(-0.03,0.03)	0.876	0.12	4.49	0.21
Linear distance_childhood	7452		0.01	(-0.03,0.05)	0.574	54.49	6.44	0.09

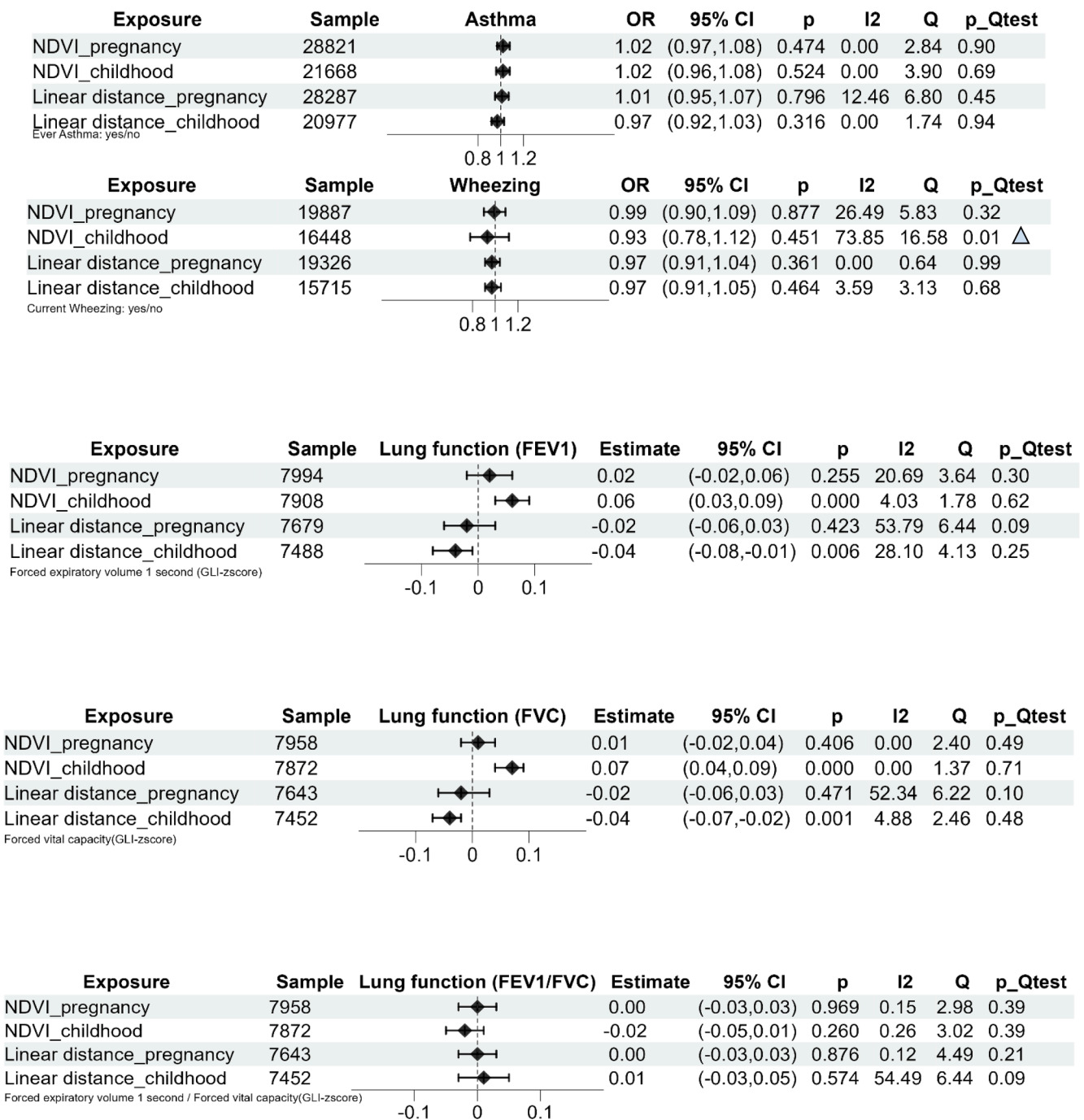Forced expiratory volume 1 second / Forced vital capacity(GLI-zscore)
-0.1 0 0.1

Fig. 2a. Pooled effect estimates from two-stage meta-analysis* for exposure to green spaces and respiratory outcomes. Regression estimates are represented per one IQR increase in each exposure.

multiple testing, no significant differences were found between lower and higher socioeconomic subgroups or based on child sex, except for lung function.

Regarding maternal education, we observed an association between NDVI around child's home with higher FEV_1 z-scores among children whose mothers reported low or medium education levels ($\beta = 0.08$, 95 % CI: 0.04;0.12, $I^2 = 0$ %, p-value < 0.001). Meanwhile, distance to a major green space was inverted associated with FEV_1-z scores, only in children from higher-maternal education strata ($\beta = -0.07$, 95 %CI: -0.12; -0.03, $I^2 = 0$ %, p-value < 0.001) (Supplementary Information, Table S7).

Similarly, increased residential surrounding green spaces during childhood was associated with higher FVC z-scores among children

whose mothers reported lower maternal education levels ($\beta = 0.08$, 95 %CI: 0.04; 0.12, $I^2 = 0$ %, p-value < 0.001). In contrast, the increased distance to green spaces was associated with lower FVC z-scores only in children from higher maternal education backgrounds ($\beta = -0.08$, 95 % CI: -0.12; -0.04, $I^2 = 0$ %, p-value < 0.001) (Supplementary Information, Table S7).

For area-level deprivation, increased residential surrounding green spaces during childhood was associated with higher FVC z-scores among children who lived in low or medium deprived areas ($\beta = 0.07$, 95 %CI: 0.03;0.1, $I^2 = 0$ %, p-value < 0.001) (Supplementary Information, Table S10). Finally, residing in greener areas during childhood was associated with higher FVC z-scores only in girls ($\beta = 0.07$, 95 %CI: 0.03; 0.12, $I^2 = 0$ %, p-value < 0.001) (Supplementary Information,
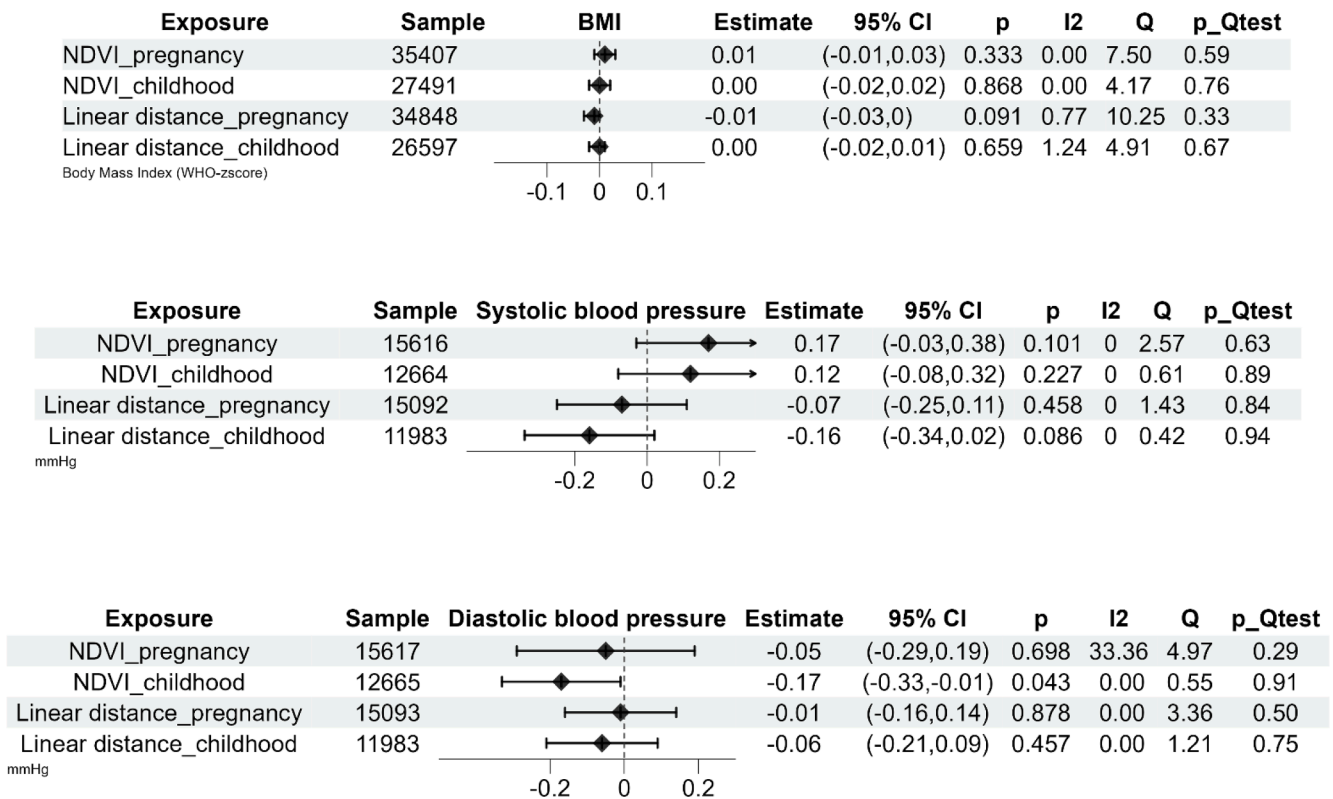
Exposure	Sample	BMI	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	35407		0.01	(-0.01,0.03)	0.333	0.00	7.50	0.59
NDVI_childhood	27491		0.00	(-0.02,0.02)	0.868	0.00	4.17	0.76
Linear distance_pregnancy	34848		-0.01	(-0.03,0)	0.091	0.77	10.25	0.33
Linear distance_childhood	26597		0.00	(-0.02,0.01)	0.659	1.24	4.91	0.67

Body Mass Index (WHO-zscore)

-0.1　0　0.1

Exposure	Sample	Systolic blood pressure	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	15616		0.17	(-0.03,0.38)	0.101	0	2.57	0.63
NDVI_childhood	12664		0.12	(-0.08,0.32)	0.227	0	0.61	0.89
Linear distance_pregnancy	15092		-0.07	(-0.25,0.11)	0.458	0	1.43	0.84
Linear distance_childhood	11983		-0.16	(-0.34,0.02)	0.086	0	0.42	0.94

mmHg

-0.2　0　0.2

Exposure	Sample	Diastolic blood pressure	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	15617		-0.05	(-0.29,0.19)	0.698	33.36	4.97	0.29
NDVI_childhood	12665		-0.17	(-0.33,-0.01)	0.043	0.00	0.55	0.91
Linear distance_pregnancy	15093		-0.01	(-0.16,0.14)	0.878	0.00	3.36	0.50
Linear distance_childhood	11983		-0.06	(-0.21,0.09)	0.457	0.00	1.21	0.75

mmHg

-0.2　0　0.2

Fig. 2b. Pooled effect estimates from two-stage meta-analysis* for exposure to green spaces and cardiometabolic outcomes. Regression estimates are represented per one IQR increase in each exposure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table S13).

We also observed some tendencies in the childhood period between more residential surrounding green spaces and higher FEV$_1$ measures in both sexes (females p = 0.004; males p = 0.008) and lower diastolic blood pressure in children from higher maternal education strata (p = 0.005) (Supplementary Information, Tables S10). There was also an inverse association between residential distance to green spaces and systolic blood pressure in males (p = 0.002) (Supplementary Information, Tables S14). However, these associations did not reach statistical significance.

3.5. Sensitivity analysis

The estimates using residential surrounding green spaces in 100 m and 500 m were similar to the main models (Supplementary Information, Figures S13-15). The associations observed for FEV$_1$ (p for 100 m buffer = 0.01; p for 500 m buffer = 0.004) and FVC z-scores (p for 100 m buffer = 0.03; p for 500 m = 0.005, respectively) maintained a similar magnitude of effect. However, these associations lost significance and exhibited increased heterogeneity when assessed at smaller buffer distances.

The 'leave-one-out' analyses confirmed the main findings without altering the pooled effect estimate for most respiratory and all cardiometabolic outcomes (Supplementary Information, Figures S16-27). The neurodevelopmental outcomes showed less consistent results. The associations regarding lung function remained consistent with similar effect sizes and low between-study heterogeneity, indicating the absence of studies that could significantly influence the outcomes as outliers (Supplementary Information, Figures S18-20). Exclusion of the DNBC cohort (Denmark) in the analysis of NDVI in childhood and current wheezing resulted in a substantial reduction of heterogeneity from 73.8 % to 0 % (OR: 1.06, 95 %CI: 0.99, 1.14) (Supplementary Information, Figures S17b). Excluding both GenR (the Netherlands) and ALSPAC (UK) decreased heterogeneity in the association between NDVI during

pregnancy and non-verbal intelligence standardized scores. However, only the exclusion of ALSPAC led to a change in the pooled effect estimate (β = 0.76, 95 %CI: −1.48; 0.03, I^2 = 0 %, p-value < 0.040), but still not statistically significant after Bonferroni correction. Moreover, the exclusion of EDEN substantially decreased I^2 from 66.9 % to 0 % (Supplementary Information, Figures S24). In the analysis of NDVI in childhood and internalization problems z-scores, excluding ALSPAC reduced heterogeneity to 0 % from 67 %, with minimal impact during the pregnancy period (Supplementary Information, Figures S25b). Lastly, the exclusion of the GenR cohort (the Netherlands) significantly reduced observed heterogeneity for NDVI in childhood and externalizing problems z-scores (β = -0.02, 95 %CI: −0.04, 0.00) (Supplementary Information, Figures S26b), while leaving EDEN (France) out reduced the heterogeneity for NDVI in pregnancy and ADHD symptoms z-score (I^2 40 % to 13 %) (Supplementary Information, Figures S27a).

Restricting our analysis to children aged 6 or older yielded unchanged results, the associations with lung function remained consistent and significant at p < 0.001 level (Supplementary Information, Table S28-S30), except for residential distance to green spaces and FVC (β = -0.04, 95 %CI: −0.07; −0.01, I^2 = 8.8 %, p-value < 0.006) (Supplementary Information, Figures S28). Applying our criteria for high between-study heterogeneity, we selected five of the 12 outcomes: NDVI during childhood and current wheezing, NDVI in both periods with non-verbal intelligence and internalizing problems, NDVI in childhood and externalizing problems, and residential distance to green spaces in childhood and ADHD symptoms (Supplementary Information, Table S16). The age of outcome assessment was independently associated with between-study heterogeneity only in the associations between NDVI during childhood and internalizing problems (β = -0.04, 95 %CI −0.05; −0.02, p < 0.001, R^2 98 %).

The sensitivity analysis revealed that excluding child age and sex as covariates for predicting lung function z-scores, BMI, and non-verbal intelligence did not alter the main results (Supplementary Information, Tables S17). The introduction of NO$_2$ and PM$_{2.5}$ into the green
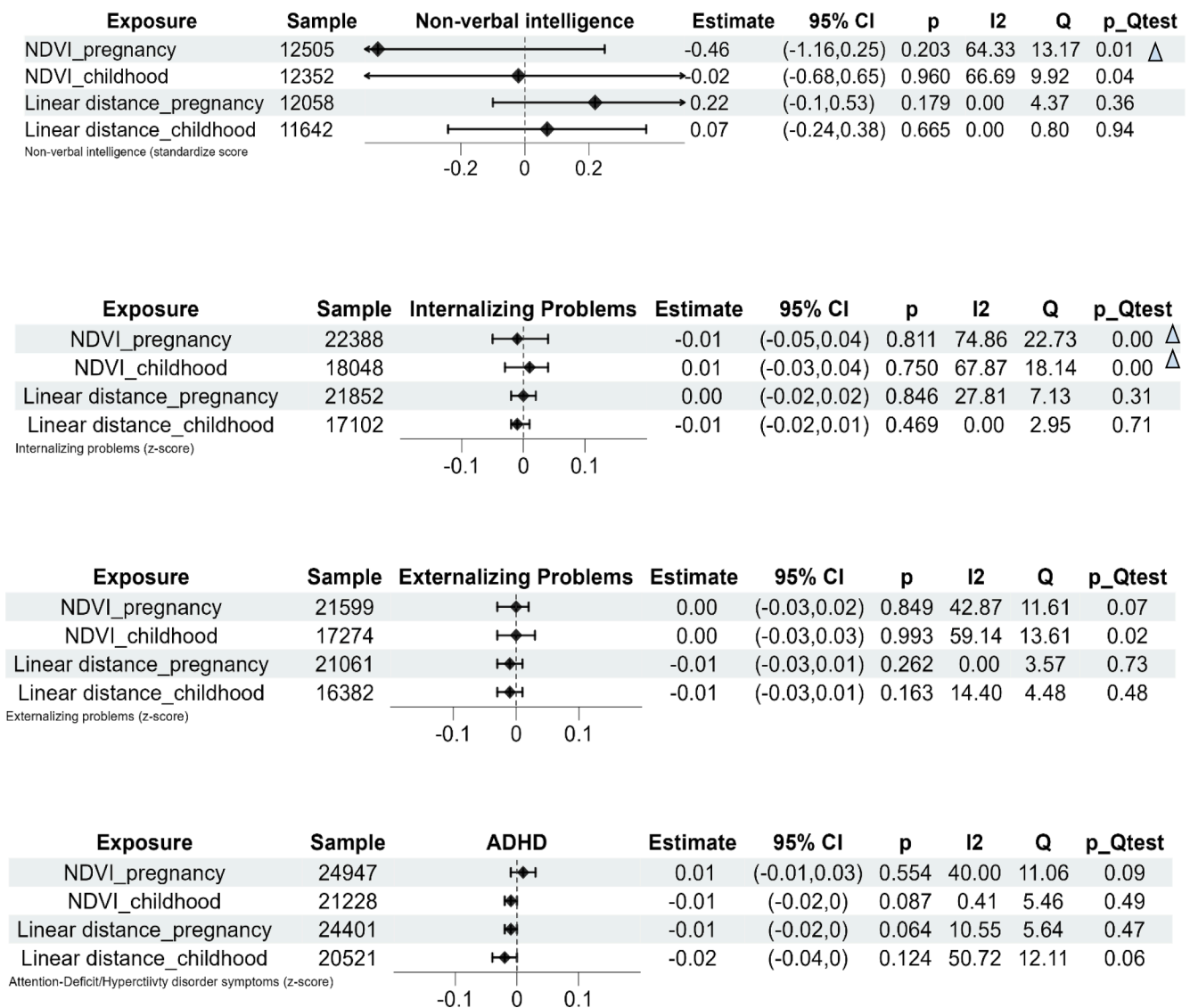
Exposure	Sample	Non-verbal intelligence	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	12505		-0.46	(-1.16,0.25)	0.203	64.33	13.17	0.01 △
NDVI_childhood	12352		-0.02	(-0.68,0.65)	0.960	66.69	9.92	0.04
Linear distance_pregnancy	12058		0.22	(-0.1,0.53)	0.179	0.00	4.37	0.36
Linear distance_childhood	11642		0.07	(-0.24,0.38)	0.665	0.00	0.80	0.94

Non-verbal intelligence (standardize score)   -0.2   0   0.2

Exposure	Sample	Internalizing Problems	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	22388		-0.01	(-0.05,0.04)	0.811	74.86	22.73	0.00 △
NDVI_childhood	18048		0.01	(-0.03,0.04)	0.750	67.87	18.14	0.00 △
Linear distance_pregnancy	21852		0.00	(-0.02,0.02)	0.846	27.81	7.13	0.31
Linear distance_childhood	17102		-0.01	(-0.02,0.01)	0.469	0.00	2.95	0.71

Internalizing problems (z-score)   -0.1   0   0.1

Exposure	Sample	Externalizing Problems	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	21599		0.00	(-0.03,0.02)	0.849	42.87	11.61	0.07
NDVI_childhood	17274		0.00	(-0.03,0.03)	0.993	59.14	13.61	0.02
Linear distance_pregnancy	21061		-0.01	(-0.03,0.01)	0.262	0.00	3.57	0.73
Linear distance_childhood	16382		-0.01	(-0.03,0.01)	0.163	14.40	4.48	0.48

Externalizing problems (z-score)   -0.1   0   0.1

Exposure	Sample	ADHD	Estimate	95% CI	p	I2	Q	p_Qtest
NDVI_pregnancy	24947		0.01	(-0.01,0.03)	0.554	40.00	11.06	0.09
NDVI_childhood	21228		-0.01	(-0.02,0)	0.087	0.41	5.46	0.49
Linear distance_pregnancy	24401		-0.01	(-0.02,0)	0.064	10.55	5.64	0.47
Linear distance_childhood	20521		-0.02	(-0.04,0)	0.124	50.72	12.11	0.06

Attention-Deficit/Hyperctilvty disorder symptoms (z-score)   -0.1   0   0.1

Fig. 2c. Pooled effect estimates from two-stage meta-analysis* for exposure to green spaces and neurodevelopmental outcomes. Regression estimates are represented per one IQR increase in each exposure. *Overall adjusted estimates with 95 % CIs from IPD meta-analyses of the outcome-specific regression models, where cohorts were assigned weights under the random-effects model (inversed variance). The dot in the plot represents the adjusted estimates, while the whiskers span the 95 % CI. Estimates represented by Odds ratio (OR) or Beta estimates and corresponding 95 % CI). Models are adjusted for: child age and sex, maternal education, area-level SES, smoking during pregnancy, parity, maternal age, and maternal BMI. Specific-cohort adjustment included maternal ethnic background and sub-cohort (city). Neurodevelopmental outcomes were further adjusted by cohort-specific instruments and /or evaluators. Sample = pooled cohorts' sample; p = p-value of statistical significance of pooled effect size; I²-statistics (I2); p_Qtest = p-value for heterogeneity Q Cochran's test.▲ τ2 95 % CI does not include zero suggesting residual heterogeneity.

spaces and lung function models resulted in minor alterations in effect sizes. While the associations preserved their direction, the statistical significance slightly diminished for NDVI and amplified with distance to green spaces. This suggests a persistent relationship between exposure to green spaces and lung function, albeit slightly moderated by air pollutants, despite the reduction in the sample size after further adjustment (Supplementary Information, Tables S18-19).

4. Discussion

To our knowledge, this is the first IPD meta-analysis study to explore the exposure to green spaces during pregnancy and childhood on various health outcomes in children of multiple European countries. The results showed that living in greener areas during childhood was associated with higher FEV$_1$ and FVC in school-age children. This association remained robust after multiple testing correction. The estimates stayed

consistent when we limited the sample to children aged 6 or older, and no single study significantly influenced the pooled estimates. While adjustments to buffer distances or accounting for pollutants resulted in minor changes in statistical significance, the overall associations persisted. Additionally, increased residential distance to green spaces was associated with lower FVC and FEV$_1$ z-scores, with statistical significance for the latter association emerging only after adjusting for traffic-related pollutants. Nevertheless, the meta-analysis did not establish clear significant associations of green spaces with asthma and wheezing, nor for cardiometabolic and neurodevelopmental outcomes.

The evidence on the effects of residential greenness on children's lung function is mixed, partly due to the scarcity of studies and the constraint of small sample sizes (Agier et al., 2019; Almeida et al., 2022b; Fuertes et al., 2020; Zare Sakhvidi et al., 2023). Our study contributes to this area by incorporating information from different cohorts, offering a more comprehensive perspective. While the observed

effect sizes were relatively small, similar to a study in the UK with repeated spirometry measures in children (Fuertes et al., 2020), they could have significant public health implications at the population level.

Our understanding of how green spaces influence lung function remains incomplete. Green spaces mitigate air pollution, potentially reducing inflammation and tissue damage in the respiratory system (Fuertes et al., 2020; Markevych et al., 2017). Our study found no significant changes in estimates after adjusting for $PM_{2.5}$ and NO_2, suggesting these pollutants did not confound the associations, as observed in a cross-sectional study with ten-year-old children in Portugal (Almeida et al., 2022b). Additionally, green spaces may expose children to beneficial microbiota, contributing to immune system development, which in turn, could influence lung function development (Markevych et al., 2017). Lastly, green spaces near home likely reflect the presence of play areas that encourage physical activity (Zare Sakhvidi et al., 2023) ultimately benefiting the respiratory system by enhancing respiratory muscle endurance and promoting lung volume growth (Wanrooij et al., 2014). This specific mechanism might involve the direct use of green spaces aligning with the phase of lung function growth (Fuertes et al., 2020), which could explain the lack of pooled effect for exposures during the pregnancy period in our study.

However, the characteristics, quality, and utilization of green spaces vary across socioeconomic levels, influenced by factors like maternal education, neighborhood deprivation, and geographical region (Maes et al., 2019; McEachan et al., 2018), potentially moderating these mechanisms. While surrounding green spaces may have positive health effects on lung function, benefiting children from all SES backgrounds, access to high-quality and safer green spaces is often influenced by family socioeconomic status and neighborhood deprivation levels (Hoffimann et al., 2017). Children from lower socioeconomic backgrounds may rely more on immediate surroundings for health benefits due to limited access to other green spaces, whereas those from higher socioeconomic backgrounds may have better access to high-quality green spaces within and beyond their neighborhoods.

Physical activity could potentially explain the sex-specific associations between green spaces and FVC. Notably, studies have demonstrated that physical activity enhances lung function specifically in girls, as evidenced by a large birth cohort study in England (Roda et al., 2020). Furthermore, various studies suggest that green spaces might be more conducive environments for promoting physical activity in girls (Fernandes et al., 2023b). However, the possibility of residual confounding by unobserved factors (such as stage of development, physiological, or anatomical factors) cannot be excluded. Additionally, this mechanism remains inconclusive, as some studies have not identified physical activity as a mediator in similar contexts (Almeida et al., 2022b; Mensink-Bout et al., 2022). We were unable to adequately test this hypothesis as harmonized data on physical activity were not available for the study sample.

In line with previous research that did not reveal an association between lifetime, ever, or current asthma and wheezing with green spaces (Dadvand et al., 2014; Fuertes et al., 2016; Parmes et al., 2020; Tischer et al., 2018; Yu et al., 2021), the lack of association could be due to exposure and outcome misclassification. The type of vegetation influences airborne particles, pollen, and allergens, which can worsen respiratory conditions like asthma and wheezing in susceptible children (Fuertes et al., 2016; Parmes et al., 2020). Despite ISAAC being commonly used in large-scale studies, the reliance on self-report measures may introduce misclassification, particularly in cross-country comparisons (Fuertes et al., 2016; Zare Sakhvidi et al., 2023).

Similarly, for cardiometabolic and neurodevelopmental outcomes our meta-analysis did not indicate an association with green space. These results align with common findings in existing literature (Jimenez et al., 2020; Luque-García et al., 2022), including a proof-of-concept study in a similar population that found inverse and null effects of exposure to NDVI during pregnancy and BMI in children (Cadman et al., 2022). Particularly for neurodevelopmental outcomes, due to the

considerable heterogeneity among cohort-specific results, a meta-analysis might not be suitable. Younger cohorts (i.e., EDEN) and cohorts with larger sample sizes (i.e., ALSPAC) influenced the results. While we have included a wide age range, this was explored by meta-regressions showing that age of outcome assessment was independently associated with between-study heterogeneity only in the associations of residential surrounding green spaces and internalizing problems. Different age groups may have distinct experiences or environmental exposures that contribute to emotional problems. It is crucial to acknowledge that missing data could significantly impact these findings. Therefore, the associations could be influenced by region-specific confounders (McEachan et al., 2018). Alternatively, there remains a possibility that our results are influenced by chance.

Our study has several strengths. It evaluated a large sample size with estimates including up to 35,407 children from 10 birth cohorts. By synthesizing data from diverse cohorts, the study benefits from a robust and varied participant pool, enhancing the generalizability of findings. Moreover, the harmonization of exposure and outcome measures across cohorts ensures data consistency and comparability, enhancing the reliability of results. We included objective and multiple measures of lung function. Evaluating various health domains, including respiratory, cardiometabolic, and neurodevelopmental aspects, offers researchers and policymakers a comprehensive perspective on the specific effects of green spaces. Understanding how a single environmental factor may impact different aspects of child health is crucial for developing nuanced recommendations and informing evidence decision-making (Vander-Weele et al., 2020). Our findings underscore the importance of integrating green spaces into urban environments for better respiratory health. Furthermore, we assessed the strength of our results through the implementation of several sensitivity analyses. Notably, the application of the federated analysis approach using DataSHIELD confers a significant advantage by allowing for consistent and reproducible analysis across multiple cohorts, while facilitating data sharing and preserving individual privacy.

The study exhibits several limitations that warrant consideration. Firstly, due to its observational nature, the establishment of definitive causal relationships between green space exposure and health outcomes remains challenging, despite rigorous adjustments for confounding variables. Nevertheless, we made efforts to establish temporal precedence by ensuring that exposures occurred before the outcomes. Secondly, missing data were addressed using complete cases as imputation methods were not available within DataSHIELD at the time of the study. Although we recognize that missing data on covariates might introduce bias into our findings, determining the direction of this bias presents a challenge. Nonetheless, both the pooled and cohort-specific associations identified in our study closely align with those observed in earlier studies assessing the impact of green spaces on respiratory (Fuertes et al., 2016; Guillien et al., 2024), cardiometabolic (Cadman et al., 2022; Vrijheid et al., 2020; Warembourg et al., 2021), and neurodevelopmental outcomes (Fernandes et al., 2023a; Julvez et al., 2021; McEachan et al., 2018). These studies involved some of the same cohorts included in our IPD meta-analysis. Thirdly, we were unable to distinguish between types of vegetation, as well as to assess the quality of the proximate areas, which appears to be relevant in the context of our study. Moreover, this study could benefit from the incorporation of spatial smoothing methods to better assess the effects of NDVI, facilitating the "borrowing of strength" across regions (Keller et al., 2015). Furthermore, it is important to acknowledge that our study was unable to measure green space exposures in non-residential settings, such as schools, which could potentially lead to exposure misclassification. The breadth of health outcomes investigated, while providing a comprehensive view, may result in variations in data quality across different domains. The limitations include variations in both measurement and availability of exposures and covariates. Despite efforts to harmonize data, disparities in measurement due to differing data collection methods may persist resulting in partially harmonized outcomes.

Therefore, we opted for a two-stage rather than a one-stage random effects meta-analysis to allow for potential heterogeneity between study areas, as also employed in similar studies (Fuertes et al., 2016; Parmes et al., 2020), mindful of the risk of splitting the data and increasing Type I error.

5. Conclusion

Exposure to green spaces in early childhood, not pregnancy, showed a robust association with better lung function, specifically higher FEV_1 and FVC measures, indicating potential respiratory health benefits for children residing in greener areas, particularly in girls. Children from both low and high-income backgrounds appeared to benefit from residential surrounding green spaces on their lung function. However, living near green spaces predominantly favored those from higher socioeconomic backgrounds. The impact of green spaces in ever asthma and current wheezing, and selected cardiometabolic and neurodevelopmental outcomes remains inconclusive. Future studies should investigate outcomes trajectories from birth to adolescence, taking into account vegetation type, green space quality, and the satisfaction levels of both children and parents with nearby green spaces.

During the preparation of this work the author used ChatGPT in order to improve language and readability. After using this tool/service, the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Amanda Fernandes: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Demetris Avraam:** Writing – review & editing, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Tim Cadman:** Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation. **Payam Dadvand:** Writing – review & editing, Conceptualization. **Mònica Guxens:** Writing – review & editing, Conceptualization. **Anne-Claire Binter:** Writing – review & editing, Conceptualization. **Angela Pinot de Moira:** Writing – review & editing, Visualization, Conceptualization. **Mark Nieuwenhuijsen:** Writing – review & editing, Conceptualization. **Liesbeth Duijts:** Writing – review & editing, Conceptualization. **Jordi Julvez:** Writing – review & editing, Conceptualization. **Montserrat De Castro:** Writing – review & editing, Data curation. **Serena Fossati:** Conceptualization. **Sandra Márquez:** Writing – review & editing. **Tanja Vrijkotte:** Writing – review & editing. **Ahmed Elhakeem:** Writing – review & editing. **Rosemary McEachan:** Writing – review & editing, Conceptualization. **Tiffany Yang:** Writing – review & editing, Conceptualization. **Marie Pedersen:** Writing – review & editing. **Johan Vinther:** Writing – review & editing. **Johanna Lepeule:** Writing – review & editing. **Barbara Heude:** Writing – review & editing. **Vincent W.V. Jaddoe:** Writing – review & editing. **Susana Santos:** Writing – review & editing. **Marieke Welten:** Writing – review & editing. **Hanan El Marroun:** Writing – review & editing. **Annemiek Mian:** Writing – review & editing. **Sandra Andrušaitytė:** Writing – review & editing. **Aitana Lertxundi:** Writing – review & editing. **Jesús Ibarluzea:** Writing – review & editing. **Ferran Ballester:** Writing – review & editing. **Ana Esplugues:** Writing – review & editing. **Maria Torres Toda:** Writing – review & editing. **Jennifer R. Harris:** Writing – review & editing. **Johanna Lucia Thorbjørnsrud Nader:** Writing – review & editing. **Giovenale Moirano:** Writing – review & editing. **Silvia Maritano:** Writing – review & editing. **Rebecca Catherine Wilson:** Writing – review & editing. **Martine Vrijheid:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108853.

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