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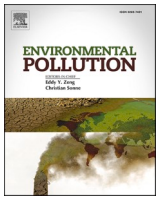

# Urban environment during pregnancy and childhood and white matter microstructure in preadolescence in two European birth cohorts☆

Anne-Claire Binter[a,b,c], Laura Granés[a,b,c,d], Elise Bannier[e,f], Montserrat de Castro[a,b,c], Sami Petricola[a,b,c], Serena Fossati[a,b,c], Martine Vrijheid[a,b,c], Cécile Chevrier[g], Hanan El Marroun[h,i], Mark Nieuwenhuijsen[a,b,c], Dave Saint-Amour[j,k], Henning Tiemeier[h,l], Mònica Guxens[a,b,c,h,*]

[a] ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[d] Department of Psychiatry, Bellvitge Biomedical Research Institute-IDIBELL, Bellvitge University Hospital, Barcelona, Spain
[e] Inria, CRNS, Inserm, IRISA UMR 6074, Empenn U1228, Univ Rennes, Rennes, France
[f] CHU Rennes, Department of Radiology, Rennes, France
[g] Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), UMR_S 1085, Rennes, France
[h] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands
[i] Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioural Sciences, Rotterdam, the Netherlands
[j] Département de Psychologie, Université du Québec à Montréal, Montréal, Québec, Canada
[k] Centre de Recherche du Centre Hospitalier Universitaire Sainte-Justine, Montréal, Québec, Canada
[l] Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, USA

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A B S T R A C T

Growing evidence suggests that urban environment may influence cognition and behavior in children, but the underlying pollutant and neurobiological mechanisms are unclear. We evaluated the association of built environment and urban natural space indicators during pregnancy and childhood with brain white matter microstructure in preadolescents, and examined the potential mediating role of air pollution and road-traffic noise. We used data of the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands (n = 2725; 2002–2006) for the primary analyses. Replication of the main findings was attempted on an independent neuroimaging dataset from the PELAGIE birth cohort, France (n = 95; 2002–2006). We assessed exposures to 12 built environment and 4 urban natural spaces indicators from conception up to 9 years of age. We computed 2 white matter microstructure outcomes (i.e., average of fractional anisotropy (FA) and mean diffusivity (MD) from 12 white matte tracts) from diffusion tensor imaging data. Greater distance to the nearest major green space during pregnancy was associated with higher whole-brain FA (0.001 (95%CI 0.000; 0.002) per 7 m increase), and higher land use diversity during childhood was associated with lower whole-brain MD (−0.001 (95%CI -0.002; −0.000) per 0.12-point increase), with no evidence of mediation by air pollution nor road-traffic noise. Higher percentage of transport and lower surrounding greenness during pregnancy were associated with lower whole-brain FA, and road-traffic noise mediated 19% and 52% of these associations, respectively. We found estimates in the same direction in the PELAGIE cohort, although confidence intervals were larger and included the null. This study suggests an association between urban environment and white matter microstructure, mainly through road-traffic noise, indicating that greater access to green space nearby might promote white matter development.

☆ This paper has been recommended for acceptance by Payam Dadvand.

* Corresponding author. Barcelona Institute for Global Health – Campus Mar, Doctor Aiguader, 88, 08003, Barcelona, Spain.
*E-mail address:* monica.guxens@isglobal.org (M. Guxens).

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## 1. Introduction

Half of the population worldwide currently lives in urbanized areas and is exposed to adverse urban environment factors, including poorer air and noise quality, and less access to natural spaces (United Nations et al., 2019). Growing evidence suggests adverse effects of air pollution, and beneficial effects of green space on child cognition and behavior (Gascon et al., 2016; HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022; Lopuszanska and Samardakiewicz, 2020; Suades-González et al., 2015; Zare Sakhvidi et al., 2022). Only few studies have investigated neurodevelopmental effects of built environment (i.e., buildings, open spaces, and infrastructures) (Binter et al., 2022a; Julvez et al., 2021; Maitre et al., 2021) and reported that higher street intersection density and land use diversity are associated with lower verbal abilities (Binter et al., 2022a).

Brain development is a complex genetically encoded process, from the very beginning of life until adulthood (Dubois et al., 2014; Giedd et al., 1999). Moreover, fetuses and children have the greatest vulnerability to the environment due to the still immature detoxification systems (Grandjean and Landrigan, 2014). Diffusion tensor imaging measures water diffusion within white matter tracts and provide information about axonal fiber tracts (van Tilborg et al., 2018). Axons develop mostly during the prenatal period, and myelination continue far into adulthood, reaching a maximum in adolescence and allowing for improved brain connectivity (Lebel and Deoni, 2018). An increase in fractional anisotropy (FA) and a decrease in mean diffusivity (MD) generally occurs with age during preadolescence (Dubois et al., 2014). Lower FA and higher MD are generally considered markers of disrupted fiber tracts and demyelination, and were associated with poorer cognitive performance (Schmithorst and Yuan, 2010) and an increased risk of psychiatric disorders (Pasi et al., 2016; White et al., 2008). White matter microstructural development is susceptible to environmental exposures, and because myelination occurs throughout pregnancy and childhood, it is important to assess environmental exposures that happen during both of these periods. Moreover, studying white matter in preadolescence may identify early markers of brain changes. Most of the few studies using diffusion tensor imaging have reported associations of air pollution during pregnancy or childhood with changes in gray and white matter of the brain structure (Cserbik et al., 2020; Guxens et al., 2018; Lubczyńska et al., 2020b), including white matter microstructure (Binter et al., 2022b; Burnor et al., 2021; Lubczyńska et al., 2020a), except one (Pujol et al., 2016). However, to our knowledge, there is no study investigating associations between built environment or urban natural spaces and white matter microstructure. Moreover, no studies have estimated whether air pollution and road-traffic noise may mediate these associations. Built environment and urban natural spaces indicators are important predictors of the levels of air pollution and road-traffic noise (Beelen et al., 2013; Eeftens et al., 2012; Fallah--Shorshani et al., 2022). Moreover, exposure to air pollution and road-traffic noise was previously found to be associated with brain alterations (Lubczyńska et al., 2020a, 2020b; Pérez-Crespo et al., 2022). Shedding light on associations between urban environment and brain development in children, and possible mediating pathways through environmental pollutants, may promote design urban and transport planning beneficial for neurodevelopment (Binter et al., 2022a).

Therefore, in this exploratory study, we aimed to identify i) associations between built environment and urban natural spaces in pregnancy and childhood, and white matter microstructure in preadolescents, and ii) potential mediating roles of air pollution and road-traffic noise in these associations. We used data from the Dutch Generation R Study for the primary analyses and attempted to replicate the main findings using the French PELAGIE cohort, the only birth cohorts to our knowledge with information on a large number of urban environmental exposures in early-life and white matter microstructure measured in preadolescence. For the mediation analyses, we focus on the air pollutants that were previously found to be associated with white matter microstructure in the Generation R Study (Lubczyńska et al., 2020a).

## 2. Methods

### 2.1. Study population

Primary analyses were performed with data from the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands (Kooijman et al., 2016). A total of 9778 women were enrolled during pregnancy, or shortly after the delivery between April 2002 and January 2006. When the children were between 9 and 12 years of age, they were invited to participate to a brain magnetic resonance imaging (MRI) session (n = 8548) (White et al., 2018). In total, 3992 attended the magnetic resonance imaging (MRI) visit. From this group, we included children from singleton pregnancies, with data on built environment and urban natural spaces exposure, and with good brain MRI data quality, resulting in a final study population of 2725 participants. Parents provided written informed consent for themselves and their children. The Medical Ethics Committee of the Erasmus Medical Center in Rotterdam, the Netherlands, granted ethical approval for the study.

Main findings were tested in an independent population-based prospective cohort, the Perturbateurs endocriniens: Etude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE) cohort in France. At early care visit, obstetricians, gynecologists, and ultrasonographers recruited 3421 women by before 19 weeks of gestation from three districts of Brittany between 2002 et 2006 (Garlantézec et al., 2009). A group of 251 children between 10 and 12 years of age was selected for an MRI sub-study. Children had to be born at term (delivery after 35 weeks of amenorrhea) and present no major condition at birth (neonatal hospitalization, hypoglycemia, or 5-min Apgar score <7), nor maternal consumption of tobacco or alcohol during pregnancy, nor medical treatment during childhood which could affect neurodevelopment (i.e., methylphenidate, psychotropic, or antiepileptic drugs, etc.) (Cartier et al., 2016). A total of 101 children were scanned. We included in this study 95 singletons with assessment of at least one built environment and urban natural spaces exposures and good quality MRI data. All parent and child participants provided written informed consent and the appropriate ethics committees approved the study.

### 2.2. Urban environment assessment

We estimated urban characteristics (i.e. built environment and urban natural spaces) and potential environmental mediators (i.e., air pollution and road-traffic noise) (de Castro et al., 2021; Guxens et al., 2022) at home addresses during pregnancy (i.e., from conception to birth) and childhood (i.e., from birth to 9 years of age).

Source data for built environment and urban natural spaces were available for the entire pregnancy, and at one time point for each year up to the MRI session. We averaged the built environment and urban natural spaces exposure levels to obtain a mean level of each exposure for each participant for the pregnancy, and for the childhood period. For children who moved within a time period, we considered the middle of the interval (i.e., trimesters of pregnancy, or year of childhood) as time of relocation for the Generation R Study while we considered the exact time of relocation for the PELAGIE cohort. We then assigned all exposures accordingly.

Detailed information about the urban environment assessment is provided in Methods S1. Briefly, as built environment indicators, we defined population density, building density, street intersection density, density of bus stops and lines, facility richness, percentage of different types of land use, land use diversity, and walkability index.

For the urban natural spaces indicators, we measured the surrounding greenness within 300 m buffer around each address, using the Normalized Difference Vegetation Index (NDVI). Furthermore, we created two indicators for residential proximity to the major urban green

and blue spaces, as they cover different aspects of natural space exposure, i.e., easy access to recreational space. We calculated access to major green space (e.g., parks or countryside) and major blue spaces (e.g., sea, lakes, fish ponds, rivers, canals) from topographical maps as the straight-line distance from the home to nearest green or blue space with an area greater than 5000 $m^2$. We also characterized the area surface of the nearest green space.

We included air pollutants that were previously found to be associated with white matter microstructure in the Generation R Study: nitrogen oxides (NOx), particulate matter with aerodynamic diameter less than 2.5 μm (PM2.5), silicon in PM2.5, zinc in PM2.5, and oxidative potential of PM2.5 measured by dithiothreitol (OPdtt) (Lubczyńska et al., 2020a).

For the road-traffic noise, in the Generation R Study, we used existing EU noise maps developed in 2012 for the municipalities of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen (Environmental Noise Directive, 2002). We used the day-evening-night level noise indicator (Lden) (Pérez-Crespo et al., 2024).

### 2.3. Magnetic resonance imaging

For the Generation R Study, images were acquired on a 3 T MR scanner (GE Healthcare, MR750W, Milwaukee, WI) using an 8-channel receive-only head coil. In the PELAGIE cohort, children underwent MRI using a 3 T MR Scanner (Magnetom Verio, VB17, Siemens Healthineers, Erlangen, Germany) using a 32-channel receiver head coil. Sequence parameters, preprocessing, and quality control procedures were published elsewhere (Cologner et al., 2019; Muetzel et al., 2015) and are provided in Methods S2.

We processed the data using the FMRIB Software Library version 5.0.9 (Jenkinson et al., 2012). We assessed average FA and MD values for 12 commonly described white matter tracts (i.e., forceps minor and forceps major, and bilateral tracts of the cingulum bundle, corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate) (Muetzel et al., 2015). We estimated whole-brain FA, and whole-brain MD using the mean of the 12 tracts. Fractional anisotropy (FA), the measured output of DTI, is a scalar value between 0 and 1 that describes the degree of anisotropy of a diffusion process, with a value of 0 indicating no restriction, or equal unrestriction, of diffusion in all directions in the brain, while a value of 1 means that diffusion is occurring in one direction only and is restricted in all other directions (Rouine et al., 2018). MD is calculated as the mean for the 3 orthogonal diffusion tensors (no unit).

### 2.4. Potential confounding variables

We identified potential confounding variables based on direct acyclic graph (DAG) from up-to-date knowledge of the scientific literature (Burnor et al., 2021; Guxens et al., 2018; Holland et al., 2023) (Fig. S1). For the Generation R cohort, we included: monthly household income, parental education, national origin, age at enrollment in the cohort, maternal smoking and alcohol use during pregnancy, parity, marital status, and parental psychological distress using the Brief Symptom Inventory (De Beurs, 2008) during pregnancy. We calculated maternal and paternal body mass index (BMI) based on weight and height measured or self-reported in the 1st trimester of pregnancy. Maternal intelligence quotient was assessed at child's age of 6 years with Raven's Advanced Progressive Matrices Test, set I (McKinzey et al., 2003). We documented child's sex from hospital records at birth and child's age at the MRI session.

For the PELAGIE cohort, we included maternal educational level, country of birth, age at enrollment in the cohort, parity, and marital status. We calculated maternal BMI based on self-reported weight and height at enrollment. Maternal intelligence quotient was assessed at child's age of 6 years with the Wechsler Adult Intelligence Scale (Wechsler, 2008). We documented child's sex at delivery and child's age at the MRI session.

### 2.5. Statistical analyses

We imputed missing potential confounding variables separately for each cohort using chained equations (Methods S3), to generate 25 imputed datasets. Percentage of missing values was below 30% except for paternal educational level (37%), paternal country of birth (32%), and paternal psychological distress (40%) in the Generation R Study. In both cohorts, included participants had different characteristics than those not included (Table S4). We applied inverse probability weighting to correct for potential attrition bias (Weisskopf et al., 2015) (Methods S4).

Exposure variables with a non-normal distribution were transformed. We calculated the interquartile range (IQR) of all exposures within the Generation R Study and standardized exposures to express estimates in both cohorts for an IQR increase. Assumptions of linear regression models were fulfilled.

We used two approaches to i) estimate associations between built environment and urban natural spaces in pregnancy and childhood, and white matter microstructure in preadolescents (i.e., single-exposure and multi-exposure analyses) and to ii) assess the mediation role of air pollution and road-traffic noise in these associations (Fig. S2).

#### 2.5.1. Primary analyses with the generation R study

*2.5.1.1. Single-exposure analyses.* We performed 64 single-exposure models using linear regressions between each built environment and urban natural spaces exposure, for pregnancy and childhood periods separately, with whole-brain FA and whole-brain MD to systematically assess the associations between each exposure independently and each outcome (equation in Method S6- part A). Models were adjusted for all covariates described above.

*2.5.1.2. Multi-exposure analyses.* We applied a variable-selection method to reduce the number of exposure variables while considering correlations between co-exposures using the Deletion-Substitution-Addition (DSA) algorithm (Methods S5) (Agier et al., 2016). DSA was chosen for its relatively low false discovery rate along with reasonable sensitivity performance, as compared to the Bonferroni-type correction or other multi-exposures approaches (Agier et al., 2016). Thus, we did not correct the single-exposure analysis with a formal multiple testing correction method and we only interpreted associations that remained in the multi-exposure models. We included all exposures in the model and forced the potential confounding variables to be present in the model, allowing only the urban exposure variables in the selection process. As DSA is based on cross-validation, we ran DSA twenty times to stabilize the results and we selected final models based on frequency of occurrence (at least 10%). We applied DSA to the 25 imputed datasets by stacking them one after the other and using weights to correct the standard errors. This method has been shown to be a reasonable approach to conduct variable selection with multiply imputed data (Wood et al., 2008). We performed separate models for the pregnancy and childhood periods of exposures (i.e., 2 models for exposures). All models had variance inflated factors smaller than 5. We calculated the effective number of outcomes by extracting eigenvalues individual level matrix of phenotype data using the poolr R package (Galwey, 2009). The effective number of outcomes was estimated to one (two outcomes = one effective test); thus, the new statistical significance level was 0.05 (0.05/1).

*2.5.1.3. Sensitivity analyses.* We ran the multi-exposure models with a minimal set of confounders available in both cohorts (i.e., maternal educational level, age at enrollment in the cohort, parity, height, body mass index, intelligence quotient, child's sex and age at the MRI).

*2.5.1.4. Mediation analyses.* We performed a mediation analysis using Valeri and Van der Weele's approach (2013) for air pollutants and road-traffic noise associated with whole-brain FA or whole-brain MD (Fig. 1). First, we identified the mediator-outcome associations (*path b* in Fig. 1) based on our previous work in Generation R Study. We included prenatal PM2.5 levels and childhood NOx levels for whole-brain FA, and prenatal concentration of silicon in PM2.5 and childhood concentrations of zinc in PM2.5 and OPdtt levels for whole-brain MD (Lubczyńska et al., 2020a). Also, we assessed the association of road-traffic noise exposure with whole-brain FA and whole-brain MD, for pregnancy and childhood periods (*path b* in Fig. 1). Next, we evaluated associations between 16 exposures (i.e., 12 built environment and 4 urban natural spaces) and 7 mediators (i.e., 5 air pollutants (2 in pregnancy and 3 in childhood) or 2 road-traffic noise variables (1 in pregnancy and 1 in childhood) (*path a* in Fig. 1). We used the multi-exposure approach described above (i.e., DSA) to reduce the number of exposures. Then, we estimated whether part of the association on whole-brain FA or whole-brain MD was mediated by air pollution or road-traffic noise (*path c* in Fig. 1). We performed mediation analyses on all imputed dataset using linear regressions for both outcome and mediator regression models, adjusting for all covariates described above and for the urban environment indicators associated with air pollution (effective number of tests from the 19 models estimated to 15 tests, statistical significance level = 0.05/15 = 0.003) or road-traffic noise (effective number of tests from the 2 models estimated to 1 test, statistical significance level = 0.05/1 = 0.05) (equation in Method S6- part B). We combined the estimates from each imputed dataset using Little and Rubin (2019) approach.

*2.5.2. Exploratory replication with the PELAGIE cohort*

For associations that were statistically significant (p-value <0.05), we used the same analytical strategy in the PELAGIE cohort.

All analyses were performed with R statistical software (version 4.0) (R Core Team, 2020). Multiple imputation, multi-exposure, and mediation analyses were performed using the mice, DSA (https://github.com/romainkp/DSA), and regmedint R packages, respectively.

## 3. Results

### 3.1. Descriptive analysis

Mothers enrolled in both cohorts were on average 31 years of age, 53.6% of them had a high education in Generation R Study and 79.8% in PELAGIE cohorts (Table 1).

Levels of urban environment indicators during pregnancy and childhood, together with their pairwise correlations, are presented in Table 2 and Fig. S3. Briefly, prenatal building density in a 300 m buffer was 0.5 $km^2/km^2$ on average in the Generation R Study, and 0.4 $km^2/km^2$ in the PELAGIE cohort. During pregnancy, participants on average lived at 200 m and 144 m of the nearest major green space in the Generation R Study and the PELAGIE cohort, respectively.

Whole-brain FA was 0.457 (min: 0.356, max: 0.513) and 0.521 (min: 0.475, max: 0.574) on average in the Generation Study and the PELAGIE cohort, respectively, and whole-brain MD was 0.809 (min: 0.667, max: 1.046) and 0.801 (min: 0.753, max: 0.842) on average in the Generation R Study and the PELAGIE cohort, respectively (Tables S5 and S6).

### 3.2. Built environment, urban natural spaces, and white matter microstructure

In the Generation R Study, greater distance to the nearest major green space during pregnancy was associated with higher whole-brain FA (0.001 (95%CI 0.000; 0.002) per 7 m increase) (Fig. 2 and Table S7). During childhood, higher land use diversity was associated with lower whole-brain MD (−0.001 (95%CI -0.002; −0.000) per 0.12-point increase) (Fig. 3 and Table S8). Both indicators remained associated in the multi-exposure models. We found similar results in models adjusted for a minimal set of confounders (Table S9).

In the PELAGIE cohort, we observed estimates in the same direction that in the Generation R Study, but with large confidence intervals including the null value (Table S10).

### 3.3. Mediation of air pollution on the associations between built environment, urban natural spaces, and white matter microstructure

Some built environment (i.e., population density, building density, density of bus lines, facility richness, land use diversity, walkability index, and percentages of commercial and industrial units, high density residential area, and transport) and urban natural indicator (i.e., NDVI in a 300 m buffer and distance to the nearest major blue space) were associated with higher prenatal PM2.5 and silicon in PM2.5 levels, or higher zinc in PM2.5, NOx and OPdtt levels during childhood (Table S10 and *path a* in Fig. 1). We found no evidence of a mediating effect of these air pollutants on the associations between built environment, urban natural spaces, and whole-brain FA and MD.

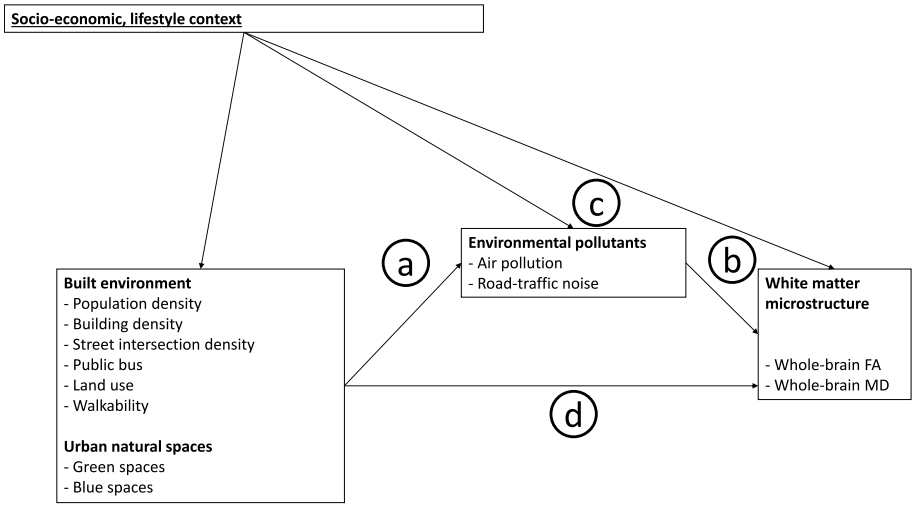


**Fig. 1.** Conceptual framework of the mediation analysis
Path c is the indirect path through paths a and b. Path d is the direct path.
FA: fractional anisotropy; MD: mean diffusivity.

**Table 1**
Population characteristics.

| | Generation R Study (N = 2725) | PELAGIE cohort (N = 95) |
|---|---|---|
| Maternal national origin | | |
| The Netherlands | 58.7 | – |
| other Western | 8.6 | – |
| non-Western | 32.7 | – |
| European | – | 100.0 |
| Paternal national origin | | |
| The Netherlands | 69.4 | – |
| other Western | 6.0 | – |
| non-Western | 24.6 | – |
| Monthly household income at enrollment | | |
| <900€ | 7.5 | – |
| 900–1600€ | 14.0 | – |
| 1600–2200€ | 14.0 | – |
| >2200€ | 64.5 | – |
| Family status at enrollment | | |
| married | 52.0 | 100.0 |
| living together | 36.9 | 0.0 |
| no partner | 11.0 | 0.0 |
| Maternal age at enrollment (years) | 31.3 ± 4.8 | 31.1 ± 3.7 |
| Paternal age at enrollment (years) | 33.6 ± 5.3 | – |
| Maternal educational level | | |
| primary or lower | 6.5 | 7.4 |
| secondary | 39.8 | 12.8 |
| higher | 53.6 | 79.8 |
| Paternal educational level | | |
| primary or lower | 5.0 | – |
| secondary | 37.5 | – |
| higher | 57.5 | – |
| Maternal pre-pregnancy BMI (kg/cm$^2$) | 23.5 ± 4.0 | 22.0 ± 3.3 |
| Paternal BMI (kg/cm$^2$) | 25.2 ± 3.3 | – |
| Maternal height (cm) | 168.1 ± 7.4 | 165.6 ± 6.6 |
| Paternal height (cm) | 182.6 ± 7.7 | – |
| Maternal psychological distress during pregnancy | 0.3 ± 0.3 | – |
| Paternal psychological distress during pregnancy | 0.1 ± 0.2 | – |
| Maternal IQ score | 98.0 ± 14.6 | 94.5 ± 10.5 |
| Maternal smoking during pregnancy | | |
| never | 78.4 | 100.0 |
| until pregnancy known | 8.3 | 0.0 |
| during pregnancy | 13.3 | 0.0 |
| Maternal alcohol use during pregnancy | | |
| no | 49.2 | 100.0 |
| <1 drink per week | 28.6 | 0.0 |
| 1–6 drinks per week | 19.1 | 0.0 |
| ≥1 drink per day | 3.1 | 0.0 |
| Maternal parity | | |
| ≥1 child | 44.2 | 67.4 |
| Child's sex | | |
| girl | 50.0 | 57.9 |
| Child's age at MRI session (years) | 10.1 ± 0.6 | 10.8 ± 0.3 |

Values are percentages for categorical variables and mean ± standard deviation for continuous variables.

We observed no association between prenatal exposure to PM2.5 and whole-brain FA in the PELAGIE cohort (0.0004 (95%CI -0.003; 0.004) per 5 μg/m$^3$ increase), therefore we did not run any mediation models.

### 3.4. Mediation of road-traffic noise on the association between built environment, urban natural spaces, and white matter microstructure

In the Generation R Study, higher prenatal road-traffic noise was associated with lower whole-brain FA (−0.001 (95%CI -0.002; −0.000 per 10 dB increase) (Table S11 and *path b* in Fig. 1).

During pregnancy, a higher percentage of transports and lower NDVI in a 100 m buffer were associated with higher road-traffic noise levels in the multi-exposure model (Table S10 and *path a* in Fig. 1). Road-traffic noise mediated 19% of the association between higher percentage of transport and lower whole-brain FA (−0.00014 (95%CI -0.0003;

**Table 2**
Urban environment characteristics.

| | Generation R Study (N = 2725) | | PELAGIE cohort (N = 95) | |
|---|---|---|---|---|
| | Pregnancy period | Childhood period | Pregnancy period | Childhood period |
| **Built environment** | | | | |
| Population density (inhabitants/km$^2$) | 3845.9 ± 668.2 | 3668.2 ± 928.2 | 2203.8 ± 2095.0 | 1814.9 ± 1683.9 |
| *Missing values* | *0%* | *0%* | *8%* | *8%* |
| Building density (km$^2$/km$^2$, 300-m buffer) | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.3 ± 0.1 | 0.2 ± 0.1 |
| Street intersection density (intersections/km$^2$, 300-m buffer) | 225.1 ± 86.2 | 201.5 ± 70.7 | 124.1 ± 62.7 | 112.3 ± 61.9 |
| *Missing values* | *0%* | *0%* | *0%* | *0%* |
| Density of bus stops (stops/km$^2$, 300-m buffer) | 7.6 ± 7.4 | 7.4 ± 6.5 | – | – |
| Density of bus lines (m/km$^2$, 300-m buffer) | 2265.5 ± 2323.8 | 2208.3 ± 1986.0 | – | – |
| *Missing values* | *0%* | *0%* | *70%* | *70%* |
| Facility richness (facility types/km$^2$, 300-m buffer) | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.0 ± 0.1 | 0.0 ± 0.0 |
| *Missing values* | *0%* | *0%* | *0%* | *0%* |
| Land use diversity (300-m buffer) | 0.5 ± 0.1 | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.4 ± 0.1 |
| *Missing values* | *0%* | *0%* | *53%* | *41%* |
| **Built environment** | | | | |
| Walkability index (300-m buffer) | 0.4 ± 0.1 | 0.3 ± 0.1 | 0.3 ± 0.1 | 0.3 ± 0.1 |
| % of high density residential land use (300-m buffer) | 36 ± 21.2 | 31.8 ± 20.3 | 10.3 ± 15.3 | 7.8 ± 11.5 |
| % of low density residential land use (300-m buffer) | 21.5 ± 20.4 | 24.9 ± 20 | 36.9 ± 22.7 | 32.7 ± 20.6 |
| % of commercial and industrial units (300-m buffer) | 5.6 ± 6.9 | 5.7 ± 6.2 | 10.1 ± 10.5 | 9.2 ± 9.3 |
| % of transport (300-m buffer) | 19.4 ± 5.9 | 18.2 ± 5.5 | 9.9 ± 6.0 | 9.0 ± 6.1 |
| *Missing values* | *0%* | *0%* | *53%* | *41%* |
| **Urban natural spaces** | | | | |
| NDVI (300-m buffer) | 0.4 ± 0.1 | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.5 ± 0.1 |
| *Missing values* | *0%* | *0%* | *1%* | *1%* |
| Distance to nearest major green space (m) | 200.1 ± 155.0 | 196.5 ± 137.6 | 144.3 ± 125.2 | 126.2 ± 116.8 |
| Distance to nearest major blue space (m) | 318.8 ± 246.5 | 341.1 ± 247.5 | 827.0 ± 509.1 | 830.7 ± 469.6 |
| Area of the nearest major green space (m$^2$) | 30897.2 ± 74541.0 | 49511.8 ± 197594.0 | 450990.3 ± 774200.1 | 394772.4 ± 493100.8 |
| *Missing values* | *0%* | *0%* | *1%* | *1%* |
| **Road-traffic noise** | | | | |
| Lden noise level (dB) | 54.7 ± 8.1 | 54.0 ± 7.2 | – | – |
| *Missing values* | *3.7%* | *2.6%* | *66%* | *65%* |
| **Air pollution** | | | | |
| NOx (μg/m$^3$) | 51.3 ± 15.0 | 47.2 ± 13.8 | – | – |
| PM2.5 (μg/m$^3$) | 17.0 ± 0.6 | 16.8 ± 0.5 | 15.7 ± 1.8 | 14.6 ± 1.0 |
| Silicon in PM2.5 (ng/m$^3$) | 92.9 ± 15.4 | 91.6 ± 15.7 | – | – |

(*continued on next page*)

**Table 2** (*continued*)

| | Generation R Study (N = 2725) | | PELAGIE cohort (N = 95) | |
|---|---|---|---|---|
| | Pregnancy period | Childhood period | Pregnancy period | Childhood period |
| Zinc in PM2.5 (ng/m$^3$) | 20.2 ± 4.2 | 20.0 ± 4.5 | – | – |
| OPdtt (nmol DTT/min/m$^3$) | 1.3 ± 0.1 | 1.3 ± 0.1 | – | – |
| *Missing values* | *0%* | *0%* | *0%* | *0%* |

Values are percentages for categorical variables and mean ± standard deviation for continuous variables.
NDVI, Normalized Difference Vegetation Index; NOx: nitrogen oxides, PM2.5: particulate matter with aerodynamic diameter less than 2.5 μm; OPdtt: oxidative potential of PM2.5 measured by dithiothreitol.

−0.00001) per 0.1-point increase) (Fig. 4 and *path c* in Fig. 1) and mediated 52% of the association between lower NDVI and lower whole-brain FA (−0.00017 (95%CI -0.0003; −0.00001) per 0.1-point increase) (Fig. 5 and *path c* in Fig. 1).

Replication analysis could not be run in PELAGIE cohort since road-traffic noise indicators were not available.

## 4. Discussion

This is the first study to examine the associations between built environment and urban natural spaces in early-life and brain white matter microstructure. Greater distance to the nearest major green space during pregnancy was associated with higher whole-brain FA, and higher land use diversity during childhood was associated with lower whole-brain MD at age 10–12 years. Importantly, we found that prenatal road-traffic noise levels mediated the association of higher percentage of transport and lower surrounding greenness with lower FA. We found estimates in the same direction in the replication cohort, but with large confidence intervals that included the null.

No previous study has investigated associations of built environment with brain structural connectivity, and very few investigated other children's health outcomes (Binter et al., 2022a; Nieuwenhuijsen et al., 2019; Siroux et al., 2018; Warembourg et al., 2021). In our study, higher land use diversity during childhood was associated with lower MD, which is generally considered an indicator of more organized white matter microstructure (Feldman et al., 2010). Land use diversity is a score based on the proportional abundance of different types of land use including artificial areas (i.e., residential, industrial, or commercial areas and artificial non-agricultural vegetated areas), agricultural areas, forest areas, and water bodies, and higher values indicate more even distributions. Higher land use diversity may indicate surrounding environment with less artificial surfaces in our study, suggesting that living in diversified land use areas during childhood is associated with lower MD in preadolescence. Nevertheless, interpretation of these types of indicators should be done carefully since they might not be comparable across cities. We found no evidence of a mediation by air pollution and road-traffic noise in the association between land use diversity and white matter microstructure, suggesting that other pathways (e.g., degree of socialization, physical activity, and stress) could explain this association (Gascon et al., 2016). A recent study on nearly 9000 children reported that both neighborhood and household contexts were associated with white matter development in children (Li et al., 2023), suggesting that urban and neighborhood quality might impact the brain development, beyond the sole exposure to air pollution and road-traffic noise. Future research is needed to better understand the influence of built environment on children's development.

We also found that some indicators of urban natural spaces, i.e., surrounding greenness and distance to the nearest major green space, were associated directly or through road-traffic noise with white matter microstructure. Specifically, greater distance to the nearest major green space during pregnancy was associated with higher FA, while higher road-traffic noise exposure mediated the association between lower surrounding greenness and lower FA. These findings seem inconsistent, since we would expect that both greater distance to the nearest major green space and lower surrounding greenness would be associated with lower FA, an indicator of less organized white matter microstructure (Feldman et al., 2010). We found moderate correlation between them, suggesting that these indicators might not be measuring the same dimension of greenness. Indeed, major green spaces are mainly dedicated to agricultural land use in our study (Fig. S4), and it is likely that distance to major green spaces is not an accurate indicator of residential exposure to urban green space. In our study, the association between surrounding greenness and FA was mediated by a reduction of road-traffic noise levels. Previous studies have suggested higher lifelong exposure to green spaces to be associated with larger gray and white matter volumes, in particular in the prefrontal cortex (Dadvand et al., 2018). This study, however, did not examine the microstructure of white matter from diffusion-weight MRI metrics. One of the possible brain mechanisms underlying the positive effects of green spaces is stress reduction (Nieuwenhuijsen et al., 2017). The Stress Reduction Theory proposes psychophysiological pathways to explain how exposure to nature induces changes in emotional state and physiological activity levels, helping stress recovery (Ulrich, 1984). Recent studies have reported that noise exposure could increase the releasing of stress hormones (Hahad et al., 2019). These hormones could influence the fetal brain development, in particular microstructural connectivity between limbic and frontotemporal networks (Lautarescu et al., 2020). Future studies are needed to understand the pathways explaining the effects of green spaces on brain.

The major strengths of this study are i) its large sample size from population-based cohorts, ii) the assessment of a large range of exposures from the urban environment with a standardized and validated protocol, iii) the common protocol to process and analyze the white matter microstructure data in two cohorts, and iv) the mediation analysis approach to understand how built environment and urban natural spaces indicators are associated with white matter microstructure. However, the study has some limitations. First, we did not have information on the time spent away from home (i.e., commuting routes, work places for pregnant women, daycare, and school for children). Our findings may thus be affected by non-differential measurement error, which could lead to underestimation of the true associations. Second, air pollution sampling campaigns were carried out when participants were between 3.5 and 9 years of age and historical pollution data were not available for all the pollutants to extrapolate the levels to the specific periods of interest. We assumed that levels of air pollution remained spatially stable over time based on previous research (Eeftens et al., 2011). Third, the sample size in the French PELAGIE cohort was small and resulted in a lack of statistical power to replicate associations. Replication with independent populations is scarce in environmental epidemiology to generalize findings, particularly for neuroimaging studies where small size samples are common. More studies are needed to provide precise estimates of the associations between urban environment and white matter microstructure and to confirm associations with meta-analyses. Fourth, we used an exploratory design as we missed strong hypotheses on the association between urban environment indicators and white matter tracts. Fifth, even if we applied inverse probability weighting to make our findings applicable to the original populations of the Generation R Study and the PELAGIE cohort, it is likely that our associations cannot be generalized to other populations, in particular more deprived populations. Sixth, mean changes in whole-brain FA and MD were relatively small. While such small changes in white matter microstructure may have little implication at the individual level, they might be relevant at the population level.

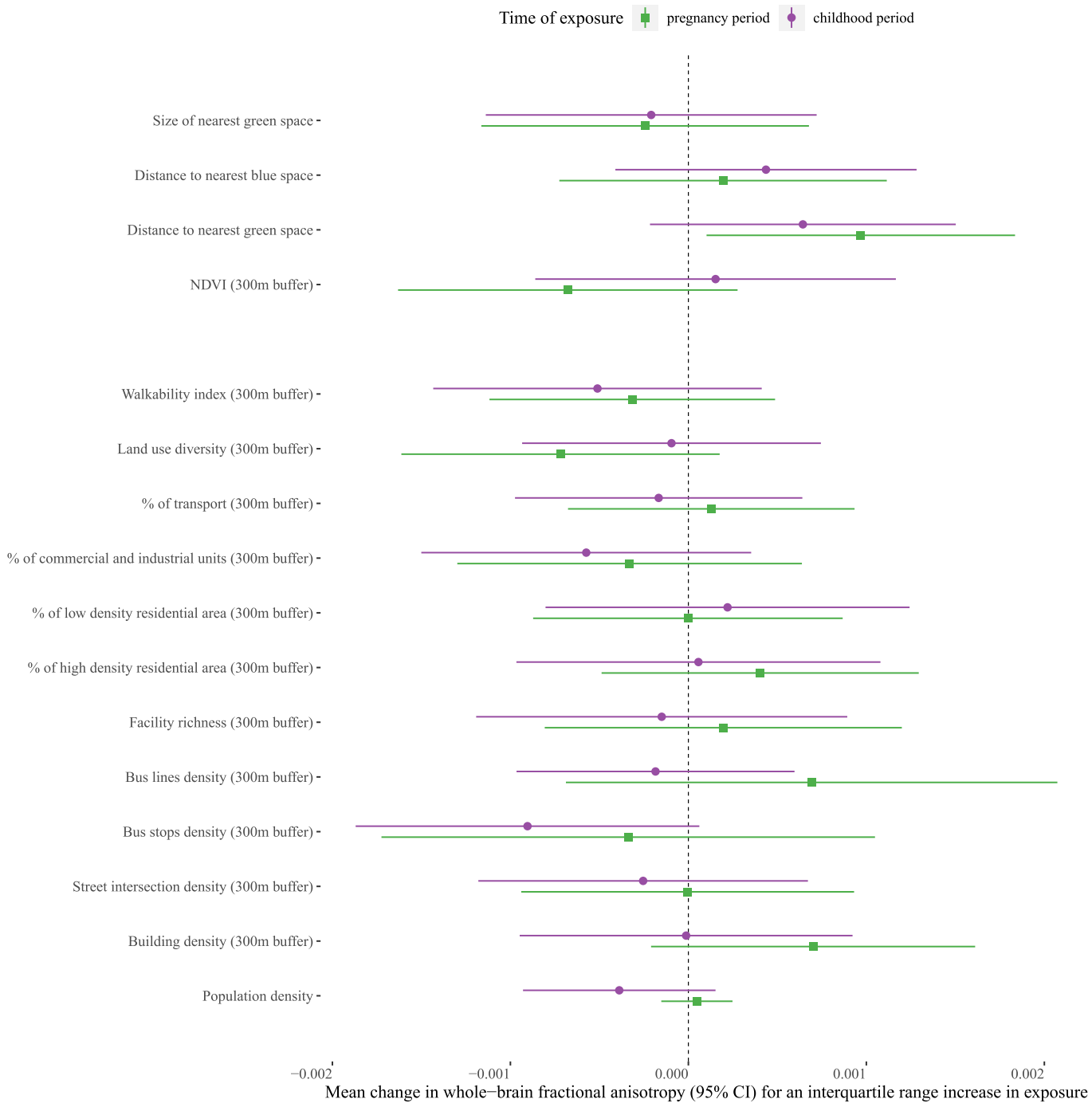


**Fig. 2.** Single-exposure associations between built environment and urban natural spaces and whole-brain fractional anisotropy in the Generation R Study at 9–12 years of age (N = 2725).
Adjusted for maternal and paternal educational levels, monthly household income, maternal and paternal national origin, maternal and paternal age at enrollment in the cohort, maternal smoking and alcohol use during pregnancy, parity, marital status, maternal and paternal psychological distress, maternal and paternal body mass index and height, maternal intelligence quotient, child's sex and age at the MRI session.
NDVI, Normalized Difference Vegetation Index.

## 5. Conclusion

Lower land use diversity, higher transport land use, greater distance to the nearest major blue space, and lower surrounding greenness in pregnancy or childhood were associated with changes in white matter microstructure in preadolescents. Moreover, we observed a mediation role of road-traffic noise. This study provides novel insights that greater access to green space nearby may reduce exposure to environmental pollutants and might be beneficial for brain structure development.

## CRediT authorship contribution statement

**Anne-Claire Binter:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Laura Granés:** Writing – review & editing, Validation. **Elise Bannier:** Writing – review & editing, Data curation. **Montserrat de Castro:** Writing – review &

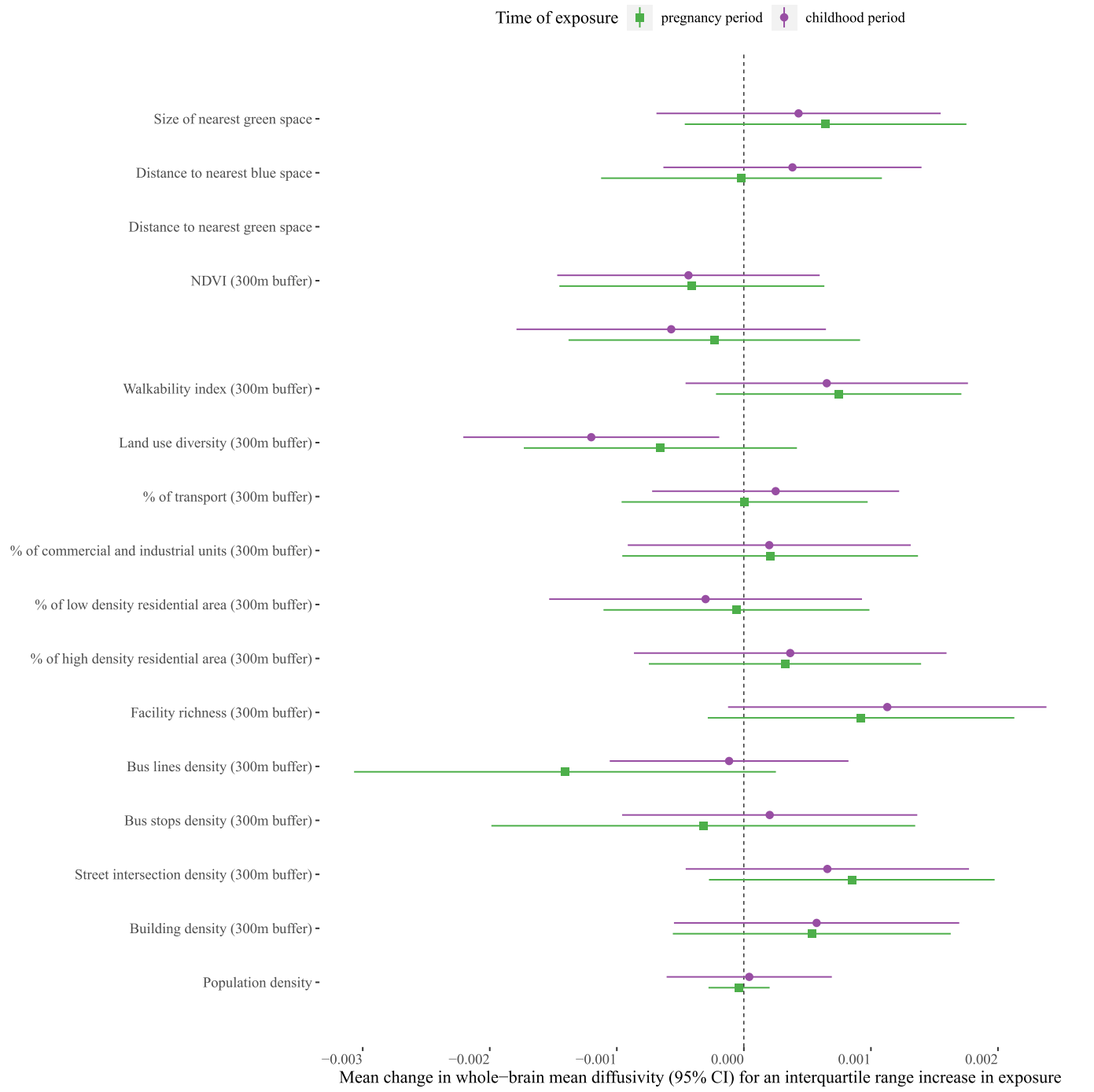


**Fig. 3.** Single-exposure associations between built environment and urban natural spaces and whole-brain mean diffusivity in the Generation R Study at 9–12 years of age (N = 2725). Adjusted for parental educational levels, monthly household income, parental national origin, parental age at enrollment in the cohort, maternal smoking and alcohol use during pregnancy, parity, marital status, parental psychological distress, parental body mass index and height, maternal intelligence quotient, child's sex and age at the MRI session.
NDVI, Normalized Difference Vegetation Index.

editing, Data curation. **Sami Petricola:** Writing – review & editing, Data curation. **Serena Fossati:** Writing – review & editing, Data curation. **Martine Vrijheid:** Writing – review & editing, Resources, Funding acquisition. **Cécile Chevrier:** Writing – review & editing, Resources, Data curation. **Hanan El Marroun:** Writing – review & editing, Methodology, Data curation. **Mark Nieuwenhuijsen:** Writing – review & editing, Methodology, Funding acquisition. **Dave Saint-Amour:** Writing – review & editing, Resources, Funding acquisition. **Henning Tiemeier:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Mònica Guxens:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition.

## 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.

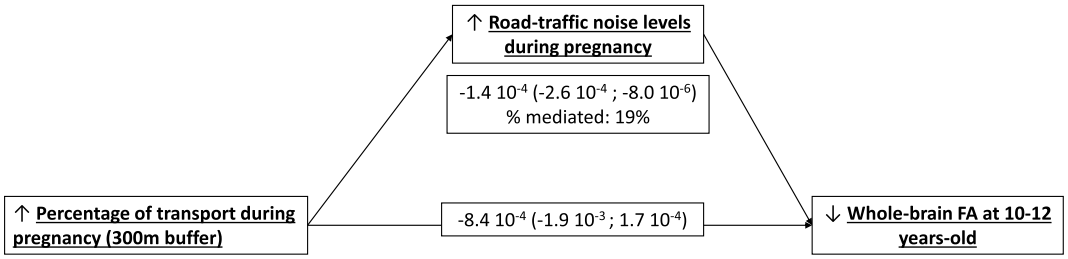


**Fig. 4.** Mediation analyses between built environment, urban natural spaces, road-traffic noise during pregnancy and whole-brain FA in the Generation R Study at 9–12 years of age (N = 2725). Adjusted for parental educational levels, monthly household income, parental national origin, parental age at enrollment in the cohort, maternal smoking and alcohol use during pregnancy, parity, marital status, parental psychological distress, parental BMI, maternal intelligence quotient, child's sex and age at the MRI session and NDVI during pregnancy.
FA: fractional anisotropy.

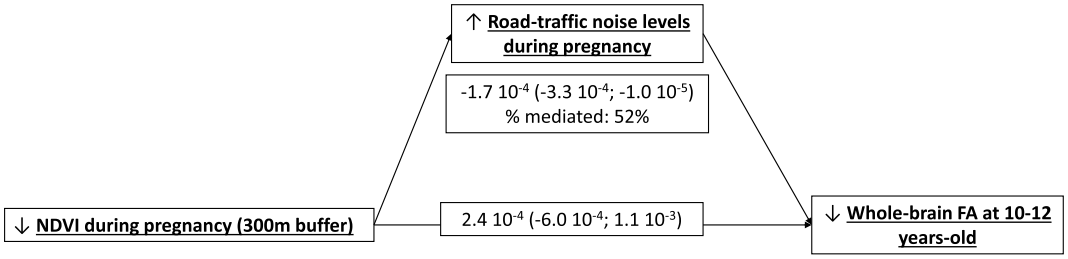


**Fig. 5.** Mediation analyses between built environment, urban natural spaces, road-traffic noise during pregnancy and whole-brain FA in the Generation R Study at 9–12 years of age (N = 2725).
Adjusted for parental educational levels, monthly household income, parental national origin, parental age at enrollment in the cohort, maternal smoking and alcohol use during pregnancy, parity, marital status, parental psychological distress, parental BMI, maternal intelligence quotient, child's sex and age at the MRI session and percentage of transport during pregnancy.
FA: fractional anisotropy; NDVI, Normalized Difference Vegetation Index.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123612.

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