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journal homepage: www.elsevier.com/locate/envpolUrban environment in early-life and brain morphology in preadolescents[☆]

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ABSTRACT

Rapid urbanization leads to increased exposure to air pollution, limited greenness, and denser built environments. However, evidence on how these urban factors influence brain development remains limited.

We investigated associations between urban characteristics during pregnancy and childhood and brain morphology in preadolescence.

The study included 2895 children from the Dutch Generation R Study, with replication in 92 children from the French PELAGIE cohort. Twelve built environment and four urban natural space indicators were estimated at residential addresses during pregnancy and childhood. Brain outcomes included cortical gray matter, cerebral white matter, cerebellum, corpus callosum, subcortical structures volumes, cortical thickness, and surface area assessed at 9–12 years. We applied multi-exposure regression models with data-driven variable selection and assessed mediation by air pollution and road-traffic noise, adjusting for confounders.

In Generation R, higher NDVI during pregnancy was associated with smaller cortical gray matter volume (-5132 mm³; 95 % CI: -8611, -1652), and higher facility richness with larger nucleus accumbens volume. During childhood, higher distance to blue space was associated with larger cortical gray matter volume, and higher transport land use with smaller hippocampus. No mediation by air pollution or road-traffic noise was observed. In PELAGIE, associations were consistent but not statistically significant. Cortical thickness was associated with several built environment indicators during childhood, and surrounding greenness was linked to smaller surface area in specific cortical regions.

Our findings suggest that early-life exposure to urban environments may influence brain morphology, with distinct contributions from green space, blue space, and built environment factors.

[☆] This paper has been recommended for acceptance by Akhgar Ghassabian.

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1. Introduction

In Europe, 75 % of the population now resides in urbanized areas, a trend that is expected to continue increasing over the coming decades (United Nations, 2022). Urban environments often expose residents to adverse environmental factors, including air and noise pollution and decreased natural spaces access. During fetal and childhood development, critical windows occur, making these periods particularly sensitive to environmental influences (Rice and Barone, 2000). Specifically, fetuses and children have immature detoxification systems that limit their ability to clear environmental pollutants efficiently. Coupled with the complexity of brain development, these vulnerabilities underscore the importance of understanding how urban exposures may impact neurodevelopmental health. Brain development begins in early gestation and continues throughout childhood, adolescence, and into young adulthood. It encompasses a complex series of processes, including neuronal proliferation, migration, and synaptic pruning, alongside myelination and other processes that shape brain morphology. Disruptions to these processes during sensitive developmental windows can lead to alterations in the brain that may affect cognition and behavior later in life.

Previous research within the Generation R Study has reported associations between prenatal air pollution exposure and alterations in brain morphology in preadolescence (Lubczyńska et al., 2020). However, less is known about how a broader range of urban environmental factors, including built environment features and access to natural spaces, may influence brain development. A few epidemiological studies have investigated the association between urban natural spaces and built environment in early-life and brain morphology in children. In a cohort of 253 school-aged children in Barcelona, Dadvand et al. found that higher surrounding greenness during childhood was associated with larger gray matter volumes in prefrontal and premotor regions, with no mediation by air pollution (Dadvand et al., 2018). In 95 Dutch adolescents, Kühn et al. showed that green open space exposure was positively associated with prefrontal gray matter volume, while tree cover was negatively associated (Kühn et al., 2023). Expanding to a broader European context, a study by Kühn et al. in 106 adolescents from multiple cities found that urban upbringing was associated with smaller hippocampal gray matter volumes compared to rural upbringing (Kühn et al., 2020). In a large US cohort (ages 9–11, $n = 7577$), Alnæs et al. showed that a pattern of urbanicity, defined by greater air pollution, low walkability, and low population density, was associated with altered white matter integrity and reduced cortical volumes and surface area (Alnæs et al., 2020). These findings point to a role of the urban environment in shaping brain morphology during development. Associations between brain morphology and cognitive-behavioral development are increasingly recognized (Luo et al., 2022) and understanding the potential impacts of urban environmental exposures on the brain is critical, as these factors may affect cognitive and behavioral development.

Air pollution and road-traffic noise were investigated as potential mediators of the association between the urban environment and brain morphology based on both empirical and biological rationale. Specific features of the built environment and natural spaces, such as higher street connectivity, traffic-related land use, or reduced vegetation, are well-established predictors of both ambient air pollution and noise levels used across Europe (Aguilera et al., 2015; Eeftens et al., 2012). For instance, areas with higher transport infrastructure tend to have higher NO₂ and PM_{2.5} concentrations and higher average noise levels, while green and blue spaces are generally associated with lower exposure levels. Biologically, these exposures may affect brain development through shared and distinct mechanisms. Green and blue spaces are thought to support neurodevelopment by reducing stress, encouraging physical activity, improving sleep, and promoting social cohesion (Gascon et al., 2016; Nieuwenhuijsen et al., 2017). In contrast, air pollution has been linked to neuroinflammation, oxidative stress, and disruption of the blood–brain barrier (Block et al., 2012). Chronic noise

exposure may also disrupt the hypothalamic-pituitary-adrenal axis, increase stress hormones, impair sleep, and affect cognitive and emotional regulation (Basner et al., 2014; Hahad et al., 2019). Investigating the pathways through which urban environmental factors, including air pollution and urban green space, might impact brain morphology could thus yield actionable insights into how urban design and transport policies could mitigate risks and support healthier neurodevelopmental outcomes.

We aimed to investigate (i) associations between specific characteristics of the urban environment, such as built environment and urban natural spaces during pregnancy and childhood, and brain morphology in preadolescents, and (ii) potential mediation of these associations by air pollution and road-traffic noise. Our primary analyses were based on data from the Dutch Generation R Study, one of the largest and most comprehensive birth cohorts to include detailed information on early-life environmental exposures and neuroimaging assessments in preadolescence. We additionally examined the French *Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance* (PELAGIE) cohort as an exploratory replication analysis to assess the consistency of associations in an independent population.

2. Methods

2.1. Design and study population

We used data from the Generation R Study, a population-based birth cohort initiated in Rotterdam, the Netherlands (Kooijman et al., 2016). The cohort included 9778 women, recruited either during their pregnancy or shortly after giving birth between 2002 and 2006. Their children were later invited to participate in a brain magnetic resonance imaging (MRI) session when they were between 9 and 12 years old (White et al., 2018). Of these, 3992 attended the MRI visit. For this analysis, we focused on 2895 children from singleton pregnancies who had available data on exposure to the built environment and urban natural spaces, along with high-quality brain MRI scans.

We replicated the key findings using an independent cohort, the PELAGIE cohort, conducted in Brittany, France, between 2002 and 2006 (Warembourg et al., 2024). Within this cohort, a subgroup of 251 children aged 10–12 years was invited for an MRI session (Binter et al., 2019). Among them, 101 children attended, and 92 singleton participants with reliable data on built environment exposure and urban natural spaces, as well as high-quality MRI data, were included in this study.

Written informed consent was obtained from all participating parents and children, and the study received ethical approval from the relevant committees.

2.2. Urban environment assessment

We considered urban characteristics, including built environment and urban natural spaces, as exposures, as well as air pollution and road-traffic noise, as potential environmental mediators. These exposures were estimated at residential addresses covering the entire pregnancy period and at one time point for each year up to the MRI session (de Castro et al., 2021; Guxens et al., 2022). We averaged the levels of the built environment and urban natural spaces characteristics to obtain the mean value of each exposure for the pregnancy and the childhood period. We used circular buffers of 300 m to capture the environmental characteristics located in a 5-min walk around homes (WHO Regional Office for Europe, 2016). For participants who relocated, we assigned exposures based on the midpoint of the time interval (i.e., trimesters for pregnancy, or years for childhood) for the Generation R Study, and the exact time of relocation for the PELAGIE cohort. We provide a detailed definition of our indicators as Methods S1 and data sources in Table S1.

In brief, we included as built environment indicators: population,

building, street intersection, bus stops, and lines density, facility diversity, percentages of land use classified as “high-density residential”, “low-density residential”, “commercial and industrial”, and “transport”, land use diversity, and walkability index. Facility richness was calculated as the number of facility types (Table S2) (i.e., business, community services, educational institutions, entertainment, financial institutions, hospitals, parks and recreation, restaurants, shopping, and transportation hubs) divided by the maximum possible number, resulting in a score between 0 and 1, where higher scores indicated greater variety of facilities (Nieuwenhuijsen et al. 2020). Land use percentages were calculated for different land use categories obtained from the Urban Atlas database for the Generation R Study and the Corine Land Cover database for the PELAGIE cohort (Nieuwenhuijsen et al. 2020). High-density residential areas were defined as continuous urban fabric, and low-density as discontinuous urban fabric. A land use diversity index was created based on the proportional abundance of each land type (i.e., urban fabric, industrial units, agricultural areas, semi-natural areas, forests, water) yielding a score between 0 and 1, with higher scores indicating a more even distribution of land types. The walkability index, calculated as the mean of the deciles of population density, street intersection density, facility richness, and land use diversity, ranged from -1 to 1 , with higher values indicating more walkable areas.

For urban natural spaces, surrounding greenness was assessed using the Normalized Difference Vegetation Index (NDVI). We also calculated the straight-line distance from the home to the nearest green or blue space and determined the surface area of the closest green space.

We included 7 air pollutants that were previously associated with brain volumes in Generation R: particulate matter (PM) with aerodynamic diameter between 2.5 and 10 μm (PMcoarse), polycyclic aromatic hydrocarbons (PAHs) in PM with aerodynamic diameter less than 2.5 μm (PM2.5), organic carbon (OC) in PM2.5, silicon in PM2.5, zinc in PM2.5, and oxidative potential of PM2.5 measured by dithiothreitol (OPdt) and electron spin resonance (OPesr) (Lubczyńska et al., 2020). Further details on measurement and modeling procedures are provided in Methods S1. In PELAGIE, air pollution data was not included due to a lack of available measurements.

Road-traffic noise in Generation R was expressed with the day-evening-night level indicator (Lden), using existing noise maps from the European Union (2012, in compliance with the Environmental Noise Directive (Environmental Noise Directive, 2002). Road-traffic noise indicators were not available in PELAGIE.

2.3. Magnetic resonance imaging

In Generation R, imaging data were collected using a 3T MR scanner (GE Healthcare, MR750W, Milwaukee, WI) equipped with an 8-channel receive-only head coil. For PELAGIE, MRI scans were performed on a 3T MR scanner (Magnetom Verio, VB17, Siemens Healthineers, Erlangen, Germany) with a 32-channel receiver head coil. Detailed sequence parameters, preprocessing steps, and quality control procedures are described in a previous publication (Lubczyńska et al., 2020) and further outlined in Methods S2.

We analyzed MRI data through the FreeSurfer (v6.0) toolbox (Fischl, 2012). We obtained volumetric measurements of all parcellated cortical gray matter areas, along with total cerebral white matter volume, corpus callosum volume, and total cerebellum volume. We also extracted volumes of 7 subcortical structures, including the thalamus, caudate nucleus, pallidum, putamen, amygdala, hippocampus, and nucleus accumbens. For each structure, the volumes of each hemisphere were combined.

In addition to these volumetric measurements, we computed surface-based morphometric data, representing cortical thickness and cortical surface area. Cortical thickness was assessed as the shortest distance between the white matter surface and the pial surface. Each vertex was labeled using the Desikan-Killiany atlas (Houston et al., 2014). Mean vertex wise analyses were available for the Generation R Study only.

2.4. Potential confounding variables

Potential confounders were selected based on the literature (Guxens et al., 2022), using a directed acyclic graph (Fig. S1). We aimed to select confounding variables as consistently as possible across the two cohorts. For Generation R, we included: monthly household income (<900; 900–1600; 1600–2200; >2.200€), parental national origin (the Netherlands, other Western, non-Western), parental age (in years) at enrollment in the cohort, parental educational level (primary; secondary; higher), parental psychological distress during pregnancy (Brief Symptom inventory (De Beurs, 2005) score), parental measured height and body mass index (BMI) during the 1st trimester of pregnancy, maternal smoking (never; until pregnancy known; during pregnancy) and alcohol use (no, <1 per week; 1–6 per week; >1 per day) during pregnancy, maternal parity (no child; ≥ 1 child), maternal marital status (married; living together; no partner), maternal intelligence quotient (Raven’s test (Raven et al., 1998) score), child’s sex (male; female) and age (in years) at the MRI session.

Some variables included in the Generation R study (e.g., monthly household income, paternal characteristics, and maternal psychological distress during pregnancy) were not available in the PELAGIE cohort. In addition, certain characteristics showed no variability in PELAGIE (e.g., all participating mothers were of European origin and married, and maternal smoking and alcohol use during pregnancy were exclusion criteria for the MRI follow-up). As a result, we included: maternal age (in years) at enrollment in the cohort, maternal educational level (primary; secondary; higher), maternal parity (no child; ≥ 1 child), maternal height and BMI (self-reported at enrollment), and maternal intelligence quotient (Wechsler Scale (Wechsler, 2008) score), child’s sex (male; female) and age (in years) at the MRI session.

2.5. Statistical analyses

To limit selection bias, we first imputed missing potential confounders using chained equations, in both cohorts (Methods S3). Then, given that included participants had higher socioeconomic status than non-MRI participants (Tables S5 and S6), we calculated the probability of participation and we weighted all analyses by the inverse of those probabilities (Methods S4).

We examined the distribution of the exposure variables and transformed non-normal distributed variables. We calculated the interquartile range (IQR) of all exposures within Generation R and used in both cohorts to obtain comparable estimates.

2.6. Main analyses with generation R

After checking assumptions for linear regression models, we first performed single-exposure linear regressions to assess associations between each exposure and each brain volume outcome. Analyses were conducted separately for the pregnancy and childhood periods and adjusted for all previously described covariates, including age at MRI scan, to account for variation in brain development. Prenatal and childhood exposures showed moderate to high correlations ranging from 0.51 to 0.96, preventing mutual adjustment. To account for head size, we additionally adjusted for intracranial volume, except in models of cortical gray matter and cerebral white matter volumes due to their high correlation with intracranial volume (>0.8). To check potential confounding by global head size, we additionally examined the associations between each exposure and intracranial volume.

Second, for each outcome, we applied a multiple-exposure linear regression model if at least one exposure showed an association in the single-exposure models (p-value <0.05). All exposures were included in the multiple-exposure model, regardless of their significance in the single-exposure models. To address multicollinearity and identify the most relevant exposures, we used the Deletion–Substitution–Addition (DSA) algorithm, which performs iterative cross-validation-based

variable selection (Methods S5). The DSA algorithm is well suited for environmental health data with correlated exposures and was selected based on its favorable performance in previous simulation studies (Agier et al., 2016).

Third, to account for multiple testing across correlated brain outcomes, we estimated the effective number of independent outcomes using the Galwey method (Cinar and Viechtbauer, 2020). This method estimates the effective number of independent tests based on the correlation structure between outcomes. This approach is particularly appropriate for neuroimaging data, where brain morphological measures are intercorrelated, and provides a more accurate control of type I error compared to conventional methods assuming test independence. From 11 correlated outcomes, we derived 7 effective tests. This number was used to calculate a Bonferroni-corrected significance threshold ($p = 0.05/7 = 0.007$), which we applied throughout the analyses.

2.7. Replication with PELAGIE

For the associations in the main analyses that were statistically significant (corrected p -value < 0.007), we attempted to replicate our findings in PELAGIE.

2.8. Follow-up analyses with Generation R

To assess whether traffic-related environmental exposures (i.e., air pollution and road-traffic noise) are in the causal paths between built environment, urban natural spaces, and brain volume outcomes, we performed a mediation analysis using the product method approach. The analysis followed a stepwise approach. First, we checked the hypothesis of mediator-outcome associations. Previous findings in Generation R found the following associations: i) higher prenatal OPesr levels and childhood OC levels with smaller corpus callosum; ii) higher PMcoarse levels and lower OPdtt levels during pregnancy with larger cerebellum; iii) higher prenatal PAHs levels and childhood OPdtt levels with smaller hippocampus; iv) higher levels of OC and PAHs levels, and lower levels of silicon in PM2.5 during pregnancy with larger amygdala; and v) higher childhood concentrations of zinc in PM2.5 with larger nucleus accumbens (Lubczyńska et al., 2020). In our study, we found no association between road-traffic noise exposure and any brain volumes for pregnancy and childhood periods (Table S7). Second, we checked the hypothesis of associations between exposures (i.e., built environment and urban natural spaces) and mediators (i.e., air pollutants). When both exposure–mediator and mediator–outcome associations were present, we proceeded with formal mediation analysis to estimate the proportion of the association between the exposures and brain volumes that could be explained by air pollution. We applied the counterfactual framework of Valeri and VanderWeele (2013), using linear regressions for both exposure–mediator and mediator–outcome regression models, and adjusting for all covariates described before.

To explore whether the global effects of the built environment and urban natural spaces were driven by localized brain changes, we analyzed regional variations in cortical thickness and surface area using a surface-based vertex-wise approach. We applied the same analytical strategy as in the main analyses, beginning with single-exposure models and followed by multiple-exposure models, adjusting for potential confounders. We corrected for multiple testing using Monte Carlo null-Z simulations with 10,000 iterations ($p < 0.001$).

All analyses were performed with R statistical software (version 4.4) (R Core Team, 2020).

3. Results

3.1. Descriptive analysis

At enrollment, mothers in both cohorts were on average 31 years of age, 53.5 % of them had a high educational level in Generation R and

81.3 % in PELAGIE (Table 1). Children were on average 10.1-year-old at the MRI assessment in Generation R and 10.9-year-old in PELAGIE, respectively. Levels and correlation structure of urban environment characteristics during pregnancy and childhood are described in Table 2 and Fig. S2, respectively. Briefly, prenatal population density in a 300m buffer was 3858 inhabitants/km² on average in Generation R, and 1249 inhabitants/km² in PELAGIE. During pregnancy, NDVI was moderate to high (0.4 in Generation R and 0.6 in the PELAGIE).

Cortical gray matter volume was on average 582,424 mm³ and 497,125 mm³ in Generation R and PELAGIE, respectively. Cortical gray matter volume correlated strongly with cerebral white matter volume (0.82 in Generation R and 0.84 in PELAGIE) and least with corpus callosum volume (0.30 in Generation R and 0.37 in PELAGIE) (Table S8).

3.2. Built environment, urban natural spaces, and brain volumes

In Generation R, in the multi-exposure models and after correction for multiple testing, higher NDVI during pregnancy was associated with smaller cortical gray matter volume (-5132 mm³ 95 %CI $(-8611; -1652)$ per 0.13 increase in NDVI) (Table 3). Higher facility richness during pregnancy was associated with larger nucleus accumbens (15.3 mm³ 95 %CI (5.6; 25.0) per 6.9 increase). During childhood, higher distance to the nearest blue space was associated with larger cortical gray matter volume (3762 mm³ 95 %CI (1620; 5903) per 8.6 m increase in distance). Higher percentage of transport land use was associated with smaller hippocampal volume (-34.9 mm³ 95 %CI $(-61.4; -8.4)$ per 6.7 increase). In supplementary analyses, we observed that higher facility richness, higher walkability index, and higher distance to the nearest major blue space were associated with larger intracranial volume (Table S9).

We found no evidence of mediation by air pollution on the associations of built environment and urban natural spaces characteristics with cortical gray matter, hippocampus, and nucleus accumbens volume (Table S10).

In PELAGIE, we did not find statistically significant associations (Table 3). We observed estimates in the same direction that in Generation R, except for higher NDVI during pregnancy, which was associated with larger cortical gray matter volume.

3.3. Built environment, urban natural spaces, and brain cortical thickness and surface area

We found no association between any urban environment indicator during pregnancy and cortical thickness. During childhood, higher percentage of high-density residential land use and of transport and higher street connectivity were associated with smaller cortical thickness in the left hemisphere pars orbitalis, right hemisphere supra-marginal, and right hemisphere cortical areas around superior temporal sulcus regions, respectively. Higher NDVI was associated with larger cortical thickness in the left hemisphere pars orbitalis region (0.03 mm 95 %CI (0.015; 0.045) per 0.13 increase in NDVI) (Fig. 1 and Table 4).

During pregnancy, higher NDVI was associated with a smaller surface area in the left hemisphere insula area and the left hemisphere superior temporal regions (e.g., surface area of the superior frontal area of the left hemisphere was -0.015 mm² smaller (95 %CI $-0.02; -0.01$) for each 0.1 increase in NDVI). Higher surrounding greenness during childhood was associated with a smaller surface area in the left superior temporal region (-0.008 mm² 95 %CI $(-0.012; -0.002)$ per 0.13 increase in NDVI) (Fig. 1 and Table 4).

4. Discussion

Our study is one of the first to investigate the associations of built environment and urban natural spaces in early-life with brain morphology. We found some associations of urban environment indicators during pregnancy and childhood with differences in brain

Table 1
Study population.

Variable	Categories	Generation R Study (N = 2895)	PELAGIE cohort (N = 92)
Maternal age at enrollment (years)		31.2 ± 4.8	30.9 ± 3.8
Paternal age at enrollment (years)		33.6 ± 5.4	–
Maternal educational level	primary or lower	173 (6.5 %)	6 (6.6 %)
	secondary	1064 (40.0 %)	11 (12.1 %)
	higher	1426 (53.5 %)	74 (81.3 %)
Paternal educational level	primary or lower	89 (4.9 %)	–
	secondary	721 (39.3 %)	–
	higher	1023 (55.8 %)	–
Monthly household income at enrollment	<900€	171 (7.5 %)	–
	900–1600€	316 (14.0 %)	–
	1600–2200€	323 (14.3 %)	–
	>2200€	1455 (64.2 %)	–
Maternal national origin	The Netherlands	1635 (57.6 %)	–
	other Western	241 (8.5 %)	–
	non-Western	961 (33.9 %)	–
Paternal national origin	Europe	–	92 (100 %)
Paternal national origin	The Netherlands	1380 (67.9 %)	–
	other Western	117 (5.8 %)	–
	non-Western	535 (26.3 %)	–
Family status at enrollment	married	1343 (50.6 %)	92 (100 %)
	living together	1017 (38.3 %)	0 (0 %)
	no partner	293 (11.0 %)	0 (0 %)
Maternal parity	no child	1586 (56.8 %)	29 (31.5 %)
	≥1 child	1207 (43.2 %)	63 (68.5 %)
Maternal smoking during pregnancy	never	1963 (77.7 %)	92 (100 %)
	until pregnancy known	346 (13.7 %)	0 (0 %)
	during pregnancy	218 (8.6 %)	0 (0 %)
Maternal alcohol use during pregnancy	no	1123 (49.1 %)	92 (100 %)
	<1 per week	661 (28.9 %)	0 (0 %)
	1–6 per week	434 (19.0 %)	0 (0 %)
	>1 per day	71 (3.1 %)	0 (0 %)
Maternal pre-pregnancy BMI (kg/m ²)		23.5 ± 4.1	21.9 ± 3.3
Paternal BMI (kg/m ²)		25.3 ± 3.4	–
Maternal height (cm)		168.1 ± 7.3	165.4 ± 6.8
Paternal height (cm)		182.4 ± 7.7	–
Maternal psychological distress during pregnancy		0.3 ± 0.3	–
Paternal psychological distress during pregnancy		0.1 ± 0.2	–
Maternal IQ score		97.8 ± 14.7	94.5 ± 10.4
Child's sex	male	1450 (50.1 %)	42 (45.7 %)
	female	1445 (49.9 %)	50 (54.3 %)
Child's age at MRI session (years)		10.1 ± 0.6	10.9 ± 0.3

Values are mean ± sd for continuous variables and number (percentage) for categorical variables. Distribution is displayed over non-imputed variables.

Table 2
Urban environment characteristics.

	Generation R Study (N = 2895)		PELAGIE cohort (N = 92)	
	Pregnancy period	Childhood period	Pregnancy period	Childhood period
Built environment				
Population density	3857.9 ± 641.4	3667.6 ± 935.5	1249.3 ± 1675.8	1050.9 ± 1373.6
Building density	0.5 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
Street intersection density ^a	225.5 ± 85.9	202.8 ± 70.7	88.6 ± 64.4	81.3 ± 58.2
Density of bus stops ^b	7.7 ± 7.9	7.5 ± 6.8	–	–
Density of bus lines ^b	2291.1 ± 2336.5	2237.2 ± 2002.4	–	–
Facility richness ^b	3.0 ± 0.0	3.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Land use diversity	0.5 ± 0.1	0.5 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
Walkability index	0.4 ± 0.1	0.3 ± 0.1	–	–
% of high-density residential land use ^a	36.0 ± 21.0	32.0 ± 20.2	1.5 ± 9.6	0.7 ± 4.7
% of low-density residential land use	21.4 ± 20.2	24.6 ± 19.9	47.8 ± 36.7	43.8 ± 33.9
% of commercial and industrial units ^b	5.7 ± 7.1	5.7 ± 6.1	–	–
% of transport	19.4 ± 5.9	18.2 ± 5.5	–	–
Urban natural spaces				
NDVI	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Distance to nearest major green space ^a	197.9 ± 154.5	195.0 ± 136.9	201.1 ± 369.8	169.2 ± 325.1
Distance to nearest major blue space ^a	324.4 ± 249	342.8 ± 250.9	6792.2 ± 4585	6631.2 ± 4637.8
Area of the nearest major green space ^c	29913.3 ± 72321.7	48847 ± 203011.4	21869211.6 ± 61435155.1	29856382.9 ± 80275166.4

NDVI, Normalized Difference Vegetation Index. Values are mean ± sd. Distribution is displayed over non-imputed, non-transformed values.

^a Square-root transformed.

^b Ln-transformed.

^c Inverse square root transformed.

Table 3
Associations of built environment and urban natural spaces with brain volumes from the multi-exposure models.

	Coef. (95 %CI)	
	Generation R Study (n = 2895)	PELAGIE cohort (n = 92)
Cortical gray matter volume		
<i>Pregnancy period</i>		
NDVI	-5132 (-8611; -1652)	17779 (4800; 30758)
<i>Childhood period</i>		
Distance to nearest blue space	3762 (1620; 5903)	4254 (-9088; 17596)
Hippocampus volume		
<i>Childhood period</i>		
% of transport land use	-34.9 (-61.4; -8.4)	-
Nucleus accumbens volume		
<i>Pregnancy period</i>		
Facility richness	15.3 (5.6; 25.0)	9.5 (-5.9; 77.5)

CI, confidence interval; Coef., coefficient; NDVI, Normalized Difference Vegetation Index. The selection of exposures was determined using the DSA (Deletion-Substitution-Addition) algorithm. DSA selections were performed separately for the prenatal and the childhood periods. Estimates are expressed as mean change for an interquartile range increase of exposure. Estimates 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. Model for cortical gray matter volume during pregnancy was additionally adjusted for low-density residential land use, models for cortical gray matter and nucleus accumbens volumes during childhood was additionally adjusted for population density (i.e., exposures selected by the DSA but not associated with the outcomes).

volumes, cortical thickness, and cortical surface area in preadolescence, in particular NDVI being associated with smaller brain volumes and surface areas, and facility richness and low-residential land use being associated with larger brain volumes and surface areas.

Our findings suggest that prenatal and childhood environmental characteristics, specifically surrounding greenness and residential land use, are associated with structural changes in both the superior and inferior frontal lobes, areas implicated in mood regulation, cognition,

and modulation of amygdala activity (Petrides et al., 2004). We also observed associations between certain urban environmental characteristics during childhood, such as proximity to blue spaces, surrounding greenness, and transport-related land use, and alterations in cortical thickness or surface area within the superior temporal lobe, a region essential for speech, language processing, and stress modulation through its connections with the amygdala (Etchell et al., 2018). Furthermore, we identified associations between environmental exposures and changes in the parietal cortex, which is critical for perception, as well as the insula, which is involved in a range of functions including perception and interoceptive awareness (Gogolla, 2017). Lastly, we found associations with two key subcortical structures: the nucleus accumbens, which plays a central role in behavioral control, and the hippocampus, essential for memory and learning (Squire, 1992; Delgado, 2007). These findings underscore the potential effect of early-life environmental exposures on brain structures that underlie cognitive, emotional, and behavioral development.

Higher prenatal NDVI was associated with smaller cortical gray matter volume, lower superior frontal and insula surface area in Generation R. This contrasts with typical physiological brain development, which is characterized by increased cortical gray matter volume (Gennatas et al., 2017) and expanded brain surface area during childhood (Kelly et al., 2023). These negative associations were not observed in PELAGIE, where greater NDVI during pregnancy was associated with larger cortical gray matter volume. In contrast, greenness exposure during childhood in Generation R showed a more expected positive pattern of brain development (Gennatas et al., 2017; Kelly et al., 2023), suggesting that the timing and type of exposure may play critical roles in shaping neurodevelopmental outcomes. These divergent results may be explained by the differences observed in correlation structures between NDVI during pregnancy and childhood within the cohorts. The moderate correlation in Generation R (0.67) may be due to the high relocation rate, compared to the very high correlation in PELAGIE (0.96). Furthermore, the unexpected negative associations in Generation R could be due to exposure to environmental pollutants associated with surrounding greenness, such as agricultural land use or increased pesticide exposure, which may act as confounding factors and negatively impact brain development. In our study, greenness was moderately negatively correlated with several air pollution indicators, suggesting

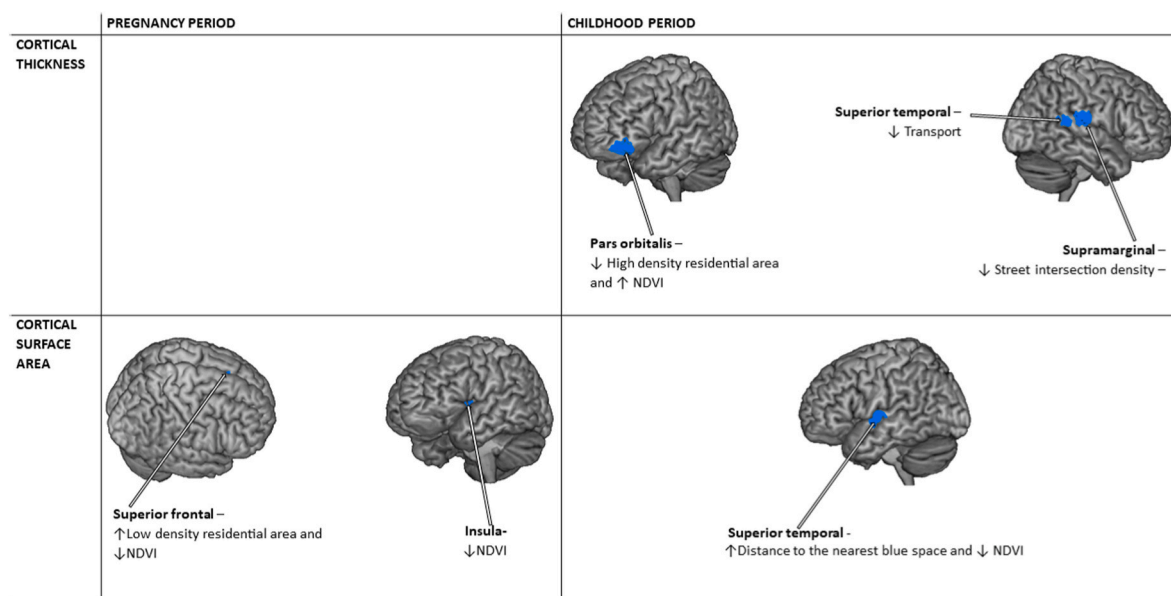


Fig. 1. Brain regions identified in the adjusted multi-exposure associations of urban environment characteristics with cortical thickness and surface area NDVI, Normalized Difference Vegetation Index. Exposures were selected using the DSA (Deletion-Substitution-Addition) algorithm, separately for the prenatal and the childhood periods. Note: the area size may not accurately represent the true value.

Table 4
Associations of built environment and urban natural spaces with brain cortical thickness and surface area from the multi-exposure models in the Generation R Study (n = 2895).

	Size of the brain region (mm)	Talairach coordinates	Coef. (95 % CI)
Left hemisphere pars orbitalis thickness	164.78	-38.2 44.9	
<i>Childhood period</i>		-11.3	
% of high-density residential land use			-0.033 (-0.048; -0.017)
Left hemisphere pars orbitalis thickness	189.32	-35.4 43.6	
<i>Childhood period</i>		-10.7	
NDVI (300m)			0.03 (0.015; 0.045)
Right hemisphere supramarginal thickness	183.20	49.9-22.0	
<i>Childhood period</i>		18.2	
Street intersection density (100m)			-0.007 (-0.01; -0.004)
Right hemisphere cortical areas around superior temporal sulcus thickness	183.62	45.8-41.9	
<i>Childhood period</i>		12.2	
% of transport			-0.019 (-0.027; -0.01)
	Size of the brain region (mm ²)	Talairach coordinates	Coef. (95 % CI)
Left hemisphere superior frontal surface area	641.37	7.8 21.0 51.9	
<i>Pregnancy period</i>			
% of low-density residential land use			0.007 (0.001; 0.013)
NDVI			-0.015 (-0.021; -0.008)
Left hemisphere insula surface area	363.01	-34.0 12.1	
<i>Pregnancy period</i>		-2.4	
NDVI			-0.007 (-0.01; -0.004)
Left hemisphere superior temporal surface area	368.05	-54.6 -8.7	
<i>Childhood period</i>		-1.1	
Distance to nearest blue space			0.004 (0.001; 0.008)
NDVI			-0.008 (-0.012; -0.002)

CI, confidence interval; Coef., coefficient; NDVI, Normalized Difference Vegetation Index. The selection of exposures was determined using the DSA (Deletion-Substitution-Addition) algorithm. DSA selections were performed separately for the prenatal and the childhood periods. Estimates are expressed as mean change for an interquartile range increase of exposure. Estimates 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.

that residual confounding by air pollution could contribute to the unexpected negative associations. Higher distance to the nearest major blue space during childhood was associated with larger cortical gray matter volume. This finding could align with the typical trajectory of cortical gray matter development (Mills et al., 2016), although no causal interpretation can be drawn in this cross-sectional study. This association may be explained by the proximity of Rotterdam with a large port

area (Abellan et al., 2024). Interestingly, we found no evidence that the effects of urban natural spaces on brain health were mediated by a reduction in air pollution or road-traffic noise, two common environmental exposures in urban settings. This suggests that other pathways, such as increased physical activity, greater opportunities for socialization, or psychological benefits associated with access to natural spaces, may play a more significant role.

Our findings align with and expand upon a small number of previous studies linking green space to brain development. Davdand et al. found that higher lifelong surrounding greenness was associated with larger gray matter volume in prefrontal regions among school-ages children, without mediation by air pollution (Dadvand et al., 2018). Similarly, Kühn et al. observed that exposure to green open space, but not tree cover, from birth to the MRI assessment was positively associated with prefrontal gray matter volume (Kühn et al., 2023). In our study, we did not distinguish between open green space and tree cover density. These findings underscore the need for future studies to better characterize urban natural spaces.

Higher transport land use during childhood was associated with brain morphological changes, specifically smaller hippocampal volume and increased superior temporal thickness, and higher street intersection density was associated with greater supramarginal thickness. These changes are contrary to typical brain development patterns in childhood (Gennatas et al., 2017), suggesting that such urban environment characteristics may negatively affect neurodevelopment. Such morphological variations may also reflect functional adaptations to complex urban environments. For example, the parietal lobe is involved in spatial attention and multimodal sensory integration (Macaluso et al., 2003), functions that may be particularly engaged in high-density urban settings. In the absence of concurrent cognitive, behavioral, or mental health measures, it remains difficult to interpret these associations as unequivocally beneficial or detrimental. While there was no statistically significant mediation by air pollution, these findings align with prior research indicating that transport-dominated areas, often proxies for more polluted environments, are harmful for brain development (Guxens et al., 2022). The positive effect of facility richness during pregnancy, such as a larger nucleus accumbens, suggests that diverse urban land uses may support healthier brain development. This is particularly noteworthy, as a previous study on the same Dutch pollution has shown that higher air pollution was associated to a smaller nucleus accumbens in preadolescence (Lubczyńska et al., 2020), suggesting the potential benefits of mixed-use areas. Additionally, we observed different patterns in brain development related to residential density at different life stages. Specifically, exposure to low-density residential land use during pregnancy was associated with a higher superior frontal surface area, while high-density residential land use during childhood were linked to lower pars orbitalis thickness. These findings suggest that living in low-density residential land use during pregnancy may support more typical brain development. This also emphasizes the importance of the timing of environmental exposure.

Our results are also consistent with prior neuroimaging studies linking urban living conditions to alterations in brain structure. Kühn et al., in a multi-city European study, found that adolescents raised in urban environments had smaller hippocampal volumes compared to those raised in rural areas (Kühn et al., 2020). This is in line with our findings about higher transport land use during childhood and smaller hippocampal volume. In addition, findings from the Adolescent Brain Cognitive Development (ABCD) study showed that children living in areas characterized by higher air pollution, low walkability, and lower population density had lower cortical surface area and volumes, along with disrupted white matter microstructure (Alnæs et al., 2020). Understanding how different urban environment characteristics affect neurodevelopment at various developmental stages could be crucial for public health and urban planning.

Various scientific studies in human, animal or in vitro studies show that brain development can be disturbed by environmental factors such

as urban exposure (Rauh and Margolis, 2016; Rannaud-Bartaire et al., 2024; Johnson et al., 2021). One potential underlying mechanisms of how urban exposure might affect normal brain development is an increase in maternal stress, leading to activation of the hypothalamic-pituitary-adrenal axis in the mother (Johnson et al., 2021). Chronic activation of the hypothalamic-pituitary-adrenal axis results in elevated cortisol levels that can cross the placental barrier. While acute cortisol release can be adaptive, chronic elevation of cortisol is associated with adverse effects on brain structure and function, especially in regions with high glucocorticoid receptor density such as the hippocampus, prefrontal cortex, and amygdala and can interfere with the maturation of these brain regions (Buss et al., 2012; Lupien et al., 2009; McEwen, 2007). In addition, urban environmental factors such as air pollution contribute to an increase in oxidative stress in the developing brain. Pollutants like PM2.5 and nitrogen oxides can enter the bloodstream, cross the blood-brain barrier, and induce neuronal inflammation by activation of microglia and damage by disrupting mitochondrial function and promoting the formation of reactive oxygen species (Andersen, 2022; Kim and Won, 2017; Charil et al., 2010; Jagtap et al., 2023). Urban exposure has also been associated with increased levels of pro-inflammatory cytokines, both systemically and within the brain. This neuroinflammatory response can affect microglial function and disrupt critical neurodevelopmental processes such as synaptic pruning, neuronal migration, and neuronal differentiation (Jayaraj et al., 2017; Ehsanifar et al., 2022). Although these studies are not directly related to humans, linking toxicology and epidemiology research can increase the understanding in the mechanism or mode of action of how urban or environmental exposures might affect brain development (Foreman et al., 2024).

One of the key strengths of this study lies in the large population size, with women recruited during early pregnancy, allowing the prospective assessment of potential confounding factors from conception to preadolescence. Additionally, the use of two independent cohorts enhances the generalizability of the findings. Second, the estimation of the urban environment, spanning multiple dimensions from conception until preadolescence, was conducted using a standardized protocol, ensuring consistency and reproducibility of the data. Third, the MRI data were processed using a harmonized protocol, reducing variability between cohorts. Fourth, we applied advanced statistical approaches, including multiple imputation and inverse probability weighting to minimize selection bias. The use of multi-exposure models accounted for potential correlations between co-exposures, and the calculation of the effective number of tests considered outcome correlations. Finally, mediation analyses allowed for the exploration of potential causal pathways.

This study comes with several limitations. First, given its smaller sample size and missing data for certain exposures, findings from PELAGIE should be interpreted with caution. Nonetheless, this complementary analysis provides insight into the robustness and generalizability of our results across different populations. Replication using independent populations is rare in neuroimaging studies, and additional studies are needed to provide more accurate estimates of the associations between urban environment and brain morphology. Additionally, the high socioeconomic position of the cohort participants may lead to an underestimation of associations, as the observed effects could be stronger in more diverse populations. The exposure assessments were conducted only at the home environment, potentially overlooking important exposures in other settings such as school or recreational areas. Thus, our exposure assessment may be subject to non-differential measurement error, potentially leading to an underestimation of the true associations. In addition, while we did not adjust for intracranial volume in the main models due to correlation with cortical gray and white matter volumes, we acknowledge that part of the observed associations may reflect variations in global brain size. Furthermore, the small effect sizes observed raise questions about the clinical relevance of the findings. Although these changes in brain morphology may have minimal significance for individuals, they could be meaningful at the

population level. Lastly, as an observational study, causal inferences cannot be drawn.

Our study provides novel evidence linking specific urban environment indicators during pregnancy and childhood with brain morphology in preadolescence. We found that greater surrounding greenness, proximity to major blue spaces, residential density, facility richness, street intersection density, and transport land use were associated with differences in brain volumes, cortical thickness, and cortical surface area. These findings suggest that early-life exposure to urban environmental factors may play a critical role in shaping brain development. Future research is warranted to replicate the findings and to explore potential implications for brain outcomes later in life. Incorporating environmental health considerations into urban planning and policy may offer valuable opportunities for promoting brain health and reducing neurodevelopmental inequalities.

CRedit authorship contribution statement

Anne-Claire Binter: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Mónica López-Vicente:** Writing – review & editing, Validation. **Sami Petricola:** Writing – review & editing, Data curation, Conceptualization. **Ellen Hessel:** Writing – review & editing, Conceptualization. **Elise Bannier:** Writing – review & editing, Data curation. **Marta Cirach:** Writing – review & editing, Data curation. **Mark Nieuwenhuijsen:** Writing – review & editing, Methodology, Funding acquisition. **Cécile Chevrier:** Writing – review & editing, Resources, Data curation. **Martijn van den Heuvel:** Writing – review & editing. **Martine Vrijheid:** Writing – review & editing, Resources, Funding acquisition. **Dave Saint-Amour:** Writing – review & editing, Resources. **Henning Tiemeier:** Writing – review & editing, Resources, Funding acquisition. **Mònica Guxens:** Writing – review & editing, Supervision, Project administration, Methodology, 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.envpol.2025.127333>.

Data availability

Data will be made available on request.

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