



Contents lists available at ScienceDirect

Environment International

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## Urban environment and cognitive and motor function in children from four European birth cohorts

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### ARTICLE INFO

Handling Editor: Olga Kalantzi

#### Keywords:

Urban environment  
Cognitive function  
Motor function  
Cohort  
Children

### ABSTRACT

**Background:** The urban environment may influence neurodevelopment from conception onwards, but there is no evaluation of the impact of multiple groups of exposures simultaneously. We investigated the association between early-life urban environment and cognitive and motor function in children.

**Methods:** We used data from 5403 mother–child pairs from four population-based birth-cohorts (UK, France, Spain, and Greece). We estimated thirteen urban home exposures during pregnancy and childhood, including: built environment, natural spaces, and air pollution. Verbal, non-verbal, gross motor, and fine motor functions were assessed using validated tests at five years old. We ran adjusted multi-exposure models using the Deletion-Substitution-Addition algorithm.

**Results:** Higher greenness exposure within 300 m during pregnancy was associated with higher verbal abilities (1.5 points (95% confidence interval 0.4, 2.7) per 0.20 unit increase in greenness). Higher connectivity density within 100 m and land use diversity during pregnancy were related to lower verbal abilities. Childhood exposure to PM<sub>2.5</sub> mediated 74% of the association between greenness during childhood and verbal abilities. Higher exposure to PM<sub>2.5</sub> during pregnancy was related to lower fine motor function (-1.2 points (-2.1, -0.4) per 3.2 µg/m<sup>3</sup> increase in PM<sub>2.5</sub>). No associations were found with non-verbal abilities and gross motor function.

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<https://doi.org/10.1016/j.envint.2021.106933>

Received 13 May 2021; Received in revised form 7 October 2021; Accepted 10 October 2021

Available online 15 October 2021

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*Discussion:* This study suggests that built environment, greenness, and air pollution may impact child cognitive and motor function at five years old. This study adds evidence that well-designed urban planning may benefit children's cognitive and motor development.

## 1. Introduction

In Europe, prevalence rates of mental disorders in children have increased by 6% in the last two decades. According to the global burden of diseases, in 2019, 7.75 per 1000 children were affected by mental disorders, and there is general concern on the possible implication of environmental factors in their onset (Grandjean and Landrigan, 2006; Institute for Health Metrics and Evaluation, 2019). Since the development of the nervous system is orchestrated from early gestation until adolescence, and the detoxification systems in prenatal and early-childhood are still immature, these periods are considered as critical windows of developmental vulnerability (Rice and Barone, 2000).

The worldwide growing urbanization is increasing the number of people exposed to a more adverse urban environment (United Nations et al., 2019), including poorer air quality, less access to natural spaces, and higher building density areas. Several epidemiological studies have found that air pollution exposure during early-life was associated with lower cognitive or motor functions (Lopuszanska and Samardakiewicz, 2020; Suades-González et al., 2015). Animal studies suggest that microglial activation and oxidative stress are potential cellular mechanisms of the effects of air pollution on the brain (Block et al., 2012). Epidemiological studies have reported that greenness exposure during early-life was associated with higher cognitive function in children (Asta et al., 2020; Dadvand et al., 2015; Liao et al., 2019). Although mechanisms of the effects of greenness exposure on the brain are poorly studied to date, some studies suggest that better air quality, increased physical activity, rising social contacts, and reduced stress may explain the observed positive effects (Nieuwenhuijsen et al., 2017). Then, some studies have reported that built environment factors (e.g., high population density, poor walkability) were associated with lower cognitive function in older adults, but to our knowledge, there are no studies in children (Besser et al., 2017; Gascon et al., 2016).

In contrast with most previous studies that have assessed single groups of exposures of urban environment, such as air pollution or greenness, evaluating multiple groups of exposures simultaneously may help disentangling confounding by co-exposures. It may highlight the mediating effects of some groups of exposures that are in the association pathway. Also, it will help revealing which urban factors are the most associated with neurodevelopment. We therefore aimed to assess i) the association between multiple groups of exposures of the urban environment during pregnancy and early-childhood, including built environment, natural spaces, and air pollution, with cognitive and motor function in children, and ii) the potential mediation of air pollution on the association between built environment and natural spaces on cognitive and motor function. Based on previous finding, we hypothesized that air pollution is associated with lower cognitive and motor function. We postulated that surrounding greenness is associated with higher cognitive function. And regarding built environment, we posit that some indicators of connectivity are associated with higher cognitive and motor function, whereas some indicators of density are associated with lower cognitive and motor function (Gascon et al., 2016; Guxens and Sunyer, 2012; Nieuwenhuijsen et al., 2017).

## 2. Material and methods

### 2.1. Study population

This study is based on the Human Early-life Exposome project (HELIX), a European consortium of six population-based birth cohorts (Maitre et al., 2018). Cohorts with neurodevelopmental assessment at

four- to five-year-old were included in the present study restricting the study population to four cohorts: Born in Bradford (BiB; Bradford, UK) (Wright et al., 2013), Etude des Déterminants pré et postnataux du développement et de la santé de l'Enfant (EDEN; Nancy and Poitiers, France) (Heude et al., 2016), Infancia y Medio Ambiente (INMA; Gipuzkoa, Sabadell, and Valencia, Spain) (Guxens et al., 2012), and Mother and Child Cohort in Crete (RHEA; Heraklion, Greece) (Chatzi et al., 2017). In the Norwegian Mother and Child Cohort Study (MoBa) cohort, cognitive and motor function were assessed by parent's reports of the Child Development Inventory, and were not comparable to the other cohorts (Magnus et al., 2016). Mother-child pairs were recruited from the general population from 2003 to 2010 at early prenatal care visit (during the first trimester for INMA and RHEA, during the first and second trimesters for EDEN, and during the second and third trimesters for BiB). Children were followed at similar ages from pregnancy through childhood. We included singleton children with urban exposure data available (13,954 children). We further excluded children who were missing for all cognitive or motor scores (from 26% for INMA to 61% in BiB) resulting in 5,403 children (Appendix, Figure S.1). Each cohort obtained approval from national ethics committees and all participating women provided informed written consent.

### 2.2. Urban environment assessment

Assessment of the urban environment (i.e. built environment, natural spaces, and air pollution) was conducted using a geographic information system (GIS)-based environmental model built for the whole HELIX study area. Exposures were assigned to the home addresses during pregnancy (from conception to birth) and for the year before the cognitive and motor assessment (hereafter referred as "childhood"). The detailed description of the exposure assessment can be found in Robinson et al. (2018). Sources of data for each exposure are summarized in Supplementary material, Table S1.

Briefly, for built environment indicators, we obtained topological maps from local authorities or from Europe-wide sources. We calculated population density as the number of inhabitants per square kilometer at the home address (from 100 m × 100 m raster). We calculated building density within 100 and 300 m buffers by dividing the area of building cover (m<sup>2</sup>) by the area of buffer (km<sup>2</sup>). We considered facility density as the number of facilities present divided by the area of the 300 m buffer. We built a facility richness index as the number of different facility types present divided by the maximum potential number of facility types specified, in a buffer of 300 m, giving a score of 0 to 1. Types of facilities are described in Table S2. We took the land use Shannon's Evenness Index as an indicator of land use diversity in urban areas, calculated as the proportional abundance of each land use type multiplied by that proportion, divided by the logarithm of the number of land use types, in a buffer of 300 m, giving a score of 0 to 1. A higher value indicates a more even distribution of land between the different types of land uses. Land uses from Urban Atlas are described in Table S3 (European Environment Agency, 2020). We defined connectivity density as the number of street intersections inside 100 and 300 m buffers, divided by the area (km<sup>2</sup>) of each buffer. We obtained bus public transport lines and stops from local authorities of each study area and from Open Street Maps when local layers were not available (Open street maps, n.d.). We calculated the density of public bus stops as the number of stops inside 100, 300, and 500 m buffers, divided by the buffer area. We used an indicator of walkability, calculated as the mean of the deciles of population density, land use diversity within 300 m buffer, street connectivity density, and facility richness index, giving a walkability score

ranging from 0 to 1 (Duncan et al., 2014; Frank et al., 2006).

For the natural spaces indicators, following the PHENOTYPE approach (Nieuwenhuijsen et al., 2014), we applied the Normalized Difference Vegetation Index (NDVI) derived from the Landsat 4–5 Thematic Mapper (TM), Landsat 7 Enhanced Thematic Mapper Plus (ETM +), and Landsat 8 Operational Land Imager (OLI)/Thermal Infrared Sensor (TIRS) with 30 m × 30 m resolution (courtesy of the U.S. Geology Survey) to measure the surrounding greenness, i.e., trees, shrubs, and parkland (Weier and Herring, 2000). NDVI quantifies greenness by measuring the difference between near-infrared (which vegetation strongly reflects) and red light (which vegetation absorbs). NDVI values range from 0 to 1, with higher numbers indicating more greenness. To achieve maximum exposure contrast, we used available cloud-free Landsat images during the period between May and August for the years relevant to our period of study and calculated greenness within 100, 300, and 500 m buffers around each address. Furthermore, an indicator for residential proximity to major natural spaces was created, as it covers different aspects of natural space exposure, i.e., easy access to recreational space. We calculated access to major green spaces (parks or countryside) and major blue spaces (sea, lakes, fish ponds, rivers, canals) from topographical maps or local sources as the straight-line distance from the home to nearest green or blue space with an area greater than 5000 m<sup>2</sup>.

For air pollutants, we assessed nitrogen dioxide (NO<sub>2</sub>) and particulate matter with an aerodynamic diameter of less than 2.5 μm (PM<sub>2.5</sub>) using land use regression (LUR) or dispersion models, temporally adjusted for measurements made in local background monitoring stations and averaged over the periods of interest. In most cases, we used site-specific LUR models developed in the context of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Beelen et al., 2013; Eeftens et al., 2012). For BiB, assessment for PM<sub>2.5</sub> was based on the ESCAPE LUR model developed in London/Oxford (UK) and adjusted for background PM<sub>2.5</sub> levels from monitoring stations in Bradford (Schembari et al., 2015). For EDEN, the ESCAPE European-wide LUR model was applied for PM<sub>2.5</sub> (Wang et al., 2014), and dispersion models were used to assess NO<sub>2</sub> exposure (Rahmali et al., 2012).

### 2.3. Cognitive and motor function assessment

Cognitive function (i.e., non-verbal and verbal abilities) and motor function (i.e., fine and gross motor) were assessed in each participating cohort using validated tests by a trained psychologist, when children were four- to five-year-old. Tests used were specific to each cohort (Table 1, and Appendix). Cognitive function was assessed with the British Picture Vocabulary Scale in the BiB cohort, with the Weschler Preschool and Primary Scale of Intelligence in the EDEN cohort, and with the McCarthy Scales of Children’s Abilities in the INMA and RHEA cohorts. Motor function was evaluated with the Clinical Kinematic Assessment Tool in the BiB cohort, with the Peg moving task for the EDEN cohort, and with the McCarthy Scales of Children’s Abilities in the INMA and RHEA cohorts. All raw scores were standardized for each study area to a mean of 100 and a standard deviation of 15 to homogenize the scales, and scores below 50 or above 150 were truncated to 50 and 150 respectively, to limit the influence of outliers (McDonald, 2009). The truncation affected less than 1% of the scores. Higher scores represent better cognitive or motor function.

### 2.4. Potential confounding variables

We identified potential confounding variables a priori using Directed Acyclic Graph based on up-to-date knowledge of the scientific literature, on data availability in each cohort, and matched as best as possible across cohorts (Hernán et al., 2004). We included information on area of inclusion (Bradford, Nancy, Poitiers, Gipuzkoa, Sabadell, Valencia, Heraklion), parental country of birth (none or one in the country of inclusion, both), deprivation index at area level of the residence (less

**Table 1**  
Description of the neurodevelopmental tests by cohort.

Cohort	Test	N assessed	Age of assessment in years (mean ± sd)	Cognitive function		Motor function	
				Verbal abilities	Non-verbal abilities	Gross motor	Fine motor
BiB, UK (N = 2,078)	British Picture Vocabulary Scale	2,057	5.0 ± 0.4	X			X
	Clinical Kinematic Assessment Tool	1,909	5.0 ± 0.4				
EDEN, France (N = 1,126)	Weschler Preschool and Primary Scale of Intelligence	1,107	5.7 ± 0.2	X	X		X
	Peg moving task	1,120	5.7 ± 0.2				
INMA, Spain (N = 1,420)	McCarthy Scales of Children’s Abilities	1,420	5.0 ± 0.7	X	X	X	X
RHEA, Greece (N = 779)	McCarthy Scales of Children’s Abilities	779	4.2 ± 0.2	X	X	X	X
N assessed				5,363	3,306	2,199	5,228

BiB, Born in Bradford; EDEN, Étude des Déterminants Pré et Postnatals du Développement et de la Santé de l’Enfant; INMA, Infancia y Medio Ambiente; RHEA, Mother-Child Cohort in Crete

deprived, deprived, most deprived), maternal age at recruitment (years), maternal educational level at recruitment (“lower than primary, primary, and lower secondary”, “upper secondary, and post-secondary non-tertiary”, “tertiary”), maternal pre-pregnancy body mass index ( $\text{kg}/\text{m}^2$ ), parity (nulliparous, one, at least two children), maternal smoking during pregnancy (no, yes), paternal age at recruitment (years), paternal educational level at recruitment (“lower than primary, primary, and lower secondary”, “upper secondary, and post-secondary non-tertiary”, “tertiary”), paternal body mass index at recruitment (less than 25, 25–29,  $\geq 30 \text{ kg}/\text{m}^2$ ), season of child birth (winter, spring, summer, autumn), child sex (female, male), and child age at assessment (days). Deprivation index at area level was described using deprivation indexes from each country, including income level, employment rate, educational level, and categorized into tertiles. Details about data sources are provided in Table S4.

## 2.5. Statistical analyses

Continuous exposure variables with a non-normal distribution were transformed to approach normality using a Box-Cox power transformation approach. All continuous exposures were standardized by the interquartile range (IQR) to express all estimates as the mean change in outcome score for an IQR increase in exposure level.

Missing data for all potential confounding variables and exposures among all participants with available data on at least one outcome variable were imputed using the chained equations method (Appendix, Table S5). We generated two sets of twenty imputed datasets, one for cognitive outcomes and one for motor outcomes, used in all of the analyses mentioned hereafter. Rubin’s rules were used to aggregate the results from the twenty imputed datasets (Little and Rubin, 2019).

## 2.6. Single-exposure analysis

We first performed single-exposure models using linear regressions for quantifying systematically the association between each exposure independently and each outcome, pooling the data of all areas and adjusting for area (i.e., mega-analysis). Models were adjusted for potential confounding variables described in the previous subsection. The assumptions of the linear regression models, including linearity between each exposure and each outcome, were fulfilled.

## 2.7. Multi-exposure analysis

Second, we applied multiple-exposure models with the outcomes

that were associated with urban exposures, to correct for multiple testing while considering the correlation between co-exposures. We only included the indicators of built environment and natural spaces as we considered air pollution as a possible mediator. We built a separate multi-exposure model with air pollution (Fig. 1) using the Deletion-Substitution-Addition (DSA) algorithm (Appendix) (Agier et al., 2016). To assure the adjustment for all potential confounding variables in each model, we fixed the potential confounding variables, allowing only the urban exposure variables to participate in the selection process. As DSA is based on cross-validation, we ran DSA two hundred times to stabilize the results and we selected final models based on frequency of occurrence (at least 10%). DSA is a selection method aiming to minimize root-mean-square error, it is possible that non-statistically significant exposures (i.e.,  $p > 0.05$ ) are kept in the models. When more than one exposure was selected by the DSA, we ran linear regression models that included all the selected exposures with a backward elimination method to only retain the exposures that were associated with the outcome ( $p < 0.05$ ). When we observed associations between prenatal and childhood period for the same exposure, we put the two indicators in the same model to disentangle their effects unless they had a correlation greater than 0.8, to avoid collinearity.

## 2.8. Mediation analysis

Third, when we observed 1) associations of urban environment with air pollution, 2) of urban environment and air pollution with the same outcome, and 3) urban environment was not used to model air pollution (Beelen et al., 2013; Eeftens et al., 2012), we applied mediation analysis for estimating whether part of the urban environment effect was mediated by air pollution (Valeri and VanderWeele, 2013). We used linear regressions for both outcome regression and mediator regression models on the twentieth imputed dataset. Standard errors were calculated using bootstrapping. We estimated the natural direct effect, the natural indirect effect, and the total effect. We also calculated the proportion mediated as the natural indirect effect/total effect.

All statistical data from all areas were pooled in a mega-analysis to increase statistical power, avoid assumptions of within-area normality and known within-area variance, and assuming homogeneity of the estimates between areas. To confirm the validity of mega-analysis, for exposures included in the multi-exposure models, we analyzed associations separately for each area, and area-specific effect estimates were combined using inverse variance-weighted random-effects meta-analyses with the Der Simonian-Laird estimator (Smith-Warner et al., 2006). We assessed heterogeneity in the estimates using the  $I^2$  statistic.

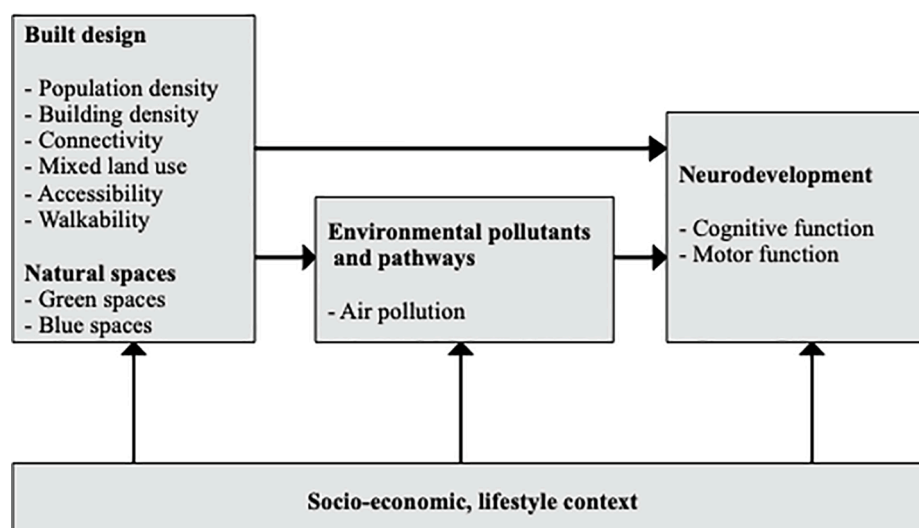


Fig. 1. Conceptual framework of analysis. Blue spaces: sea, lakes, fish ponds, rivers, canals. Green spaces: parks, countryside.

We did not interpret the associations of the mega-analysis in case of heterogeneity across areas.

All analyses were performed with R statistical software (version 4.0; R Development Core Team), using the mice package for multiple imputation, DSA for the DSA algorithm, regmedint for mediation, and ggplot2 for drawing plots.

### 3. Results

#### 3.1. Study population

Urban environment, and socioeconomic characteristics overall and by area are described in Table 2 and Appendix, Table S6. Based on observed values, parents of participants were more likely to be born in the country of inclusion, were older, and with a higher educational level compared to parents of children that did not participate to the neuro-assessments (Appendix, Table S7). Levels of exposure during pregnancy and childhood, together with their pairwise correlations, are presented in Table 3, and Appendix, Table S6, Figure S2, and Figure S3. Briefly, NDVI during pregnancy and childhood was negatively correlated with indicators of population density and air pollution ( $\rho$  from -0.27 to -0.75). Land use diversity was positively correlated with building density, facility density, and density of public bus stops ( $\rho$  from 0.31 to 0.73). Urban environment indicators during pregnancy vs childhood were all positively correlated (Appendix, Figure S4).

#### 3.2. Associations between urban environment and cognitive and motor scores

During pregnancy, higher land use diversity, street connectivity density in a 100 m buffer, and walkability index were associated with lower verbal scores in the single-exposure models (Fig. 2, and Appendix Table S8). Also, higher NDVI in 300 and 500 m buffers during pregnancy were associated with higher verbal abilities. In the multi-exposure models, land use diversity, street connectivity density, and NDVI in a 500 m buffer during pregnancy remained associated with verbal scores (-0.8 point (95% CI -1.4, -0.2), -0.9 point (95% CI -1.4, -0.3), and +1.5 point (95% CI 0.4, 2.7), respectively) (Table 4, and Appendix Table S9). Building density in the 100 m buffer was retained in the multi-exposure model and became statistically significant (+0.8 point (95% CI 0.1, 1.5)). We found similar results in the meta-analysis, with no heterogeneity between areas (Table 4, and Appendix, Figure S6).

During childhood, higher levels of land use diversity and walkability index were associated with lower verbal scores in the single-exposure models (Fig. 2, and Appendix, Table S8). In the multi-exposure model, higher land use diversity during childhood remained associated with lower verbal scores, with a similar beta estimate (-0.6 point (95% CI -1.1, 0)) (Table 4, and Appendix, Table S9). We did not observe heterogeneity between areas in the meta-analysis (Table 4, and Appendix, Figure S6).

We did not perform mutual adjustment for pregnancy and childhood exposures to land use diversity due to high correlations between the two periods ( $\rho = 1$ , Appendix, Figure S4).

No associations were observed between urban environment indicators during pregnancy and childhood and non-verbal abilities, gross motor, and fine motor skills (Fig. 2, Fig. 3, and Appendix, Table S8).

#### 3.3. Associations between air pollution and cognitive and motor scores

No association was observed between prenatal exposures and verbal abilities. Regarding childhood exposures, higher levels of PM2.5 during childhood were associated with lower verbal scores in the single-exposure models (-1.2 point (95% CI -2.1, -0.4)) (Fig. 2, and Appendix, Table S7), which remained in the multi-exposure model (Table 4, and Appendix, Table S9). However, the overall estimate of that association was null in the meta-analysis (0 point (95% CI -1.7, 1.6))

**Table 2**

Description of the socioeconomic and family variables included of the study population (n = 5,403 mother-child pairs).

	Distribution
<b>Parental characteristics</b>	
Parents place of birth	
None or one in the country of inclusion	1,707 (31.8%)
Both	3,654 (68.2%)
Deprivation index at area-level during pregnancy	
less deprived	1,397 (29.1%)
middle deprived	1,734 (36.2%)
most deprived	1,662 (34.7%)
Deprivation index at area-level at four- to five years old	
less deprived	1,521 (31.8%)
middle deprived	1,786 (37.3%)
most deprived	1,477 (30.9%)
Maternal age (years)	29.8 ± 5.2
Maternal educational level	
lower than primary, primary, and lower secondary	1,610 (31.0%)
upper secondary, and post-secondary non-tertiary	1,695 (32.7%)
tertiary	1,884 (36.3%)
Maternal pre-pregnancy body mass index (kg/m <sup>2</sup> )	25.4 ± 5.4
Parity	
no child	2,328 (44.2%)
1 child	1,802 (34.2%)
≥ 2 children	1,140 (21.6%)
Maternal smoking during pregnancy	
no	4,094 (78.3%)
yes	1,133 (21.7%)
Paternal age (years)	33.5 ± 5.3
Paternal educational level	
lower than primary, primary, and lower secondary	1,568 (33.0%)
upper secondary, and post-secondary non-tertiary	1,702 (35.9%)
tertiary	1,477 (31.1%)
Paternal body mass index	
less than 25 kg/m <sup>2</sup>	1,280 (42.0%)
25–29 kg/m <sup>2</sup>	1,354 (44.4%)
≥30 kg/m <sup>2</sup>	413 (13.6%)
<b>Child characteristics</b>	
Season of birth	
winter	1316 (24.5%)
spring	1369 (25.5%)
summer	1320 (24.5%)
autumn	1374 (25.5%)
Child sex	
female	2615 (48.4%)
male	2786 (51.6%)

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

**Table 3**  
Description of the urban environment variables of the study population (n = 5,403 mother–child pairs).

	Pregnancy period	Childhood period
<b>Built environment</b>		
Population density (inhabitants/km <sup>2</sup> )	6857 ± 8044	6337 ± 7721
Building density (m <sup>2</sup> /km <sup>2</sup> )		
100-m buffer	248184 ± 148598	236218 ± 147718
300-m buffer	208783 ± 127204	196929 ± 126199
Facility density (facilities/km <sup>2</sup> , 300-m buffer)	41.7 ± 60.5	35.7 ± 49.6
Facility richness (facility types/km <sup>2</sup> , 300-m buffer)	0.1 ± 0.1	0.1 ± 0.1
Land use diversity (300-m buffer)	0.5 ± 0.1	0.5 ± 0.1
Connectivity density (intersections/km <sup>2</sup> )		
100-m buffer	237.1 ± 147.3	224.3 ± 145.5
300-m buffer	186.3 ± 95.3	174.0 ± 93.1
Density of public bus stops (stops/km <sup>2</sup> )		
100-m buffer	28.6 ± 74.4	27.6 ± 80.0
300-m buffer	25.8 ± 34.9	24.9 ± 35.1
500-m buffer	22.4 ± 22.6	21.8 ± 22.9
Walkability index (300-m buffer)	0.3 ± 0.1	0.3 ± 0.1
<b>Natural spaces</b>		
NDVI		
100-m buffer	0.4 ± 0.1	0.4 ± 0.1
300-m buffer	0.4 ± 0.1	0.4 ± 0.1
500-m buffer	0.4 ± 0.1	0.4 ± 0.1
Distance to nearest major green space (m)	185 ± 160	170 ± 156
Distance to nearest major blue space (m)	1761 ± 1635	1772 ± 1634
<b>Air pollution</b>		
NO <sub>2</sub> (µg/m <sup>3</sup> )	21.7 ± 10.3	25.1 ± 11.6
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	15.3 ± 3.3	15.1 ± 2.7

NDVI, Normalized Difference Vegetation Index; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter of less than 2.5 µm. Values are mean ± sd. Distribution is displayed over non-imputed, non-transformed values.

(Table 4, and Appendix, Figure S6). We observed heterogeneity between areas, with a negative association observed for the BiB cohort (-2.7 points (95% CI -4.0, -1.4)) (Appendix, Figure S6), while no association was found for the other areas.

Exposure to PM<sub>2.5</sub> during pregnancy was associated with lower fine motor function in the single-exposure models (-1.2 point (95% CI -2.1, -0.4)) (Fig. 3, and Appendix, Table S8), which remained associated in the multi-exposure model and in the meta-analysis (Table 4, and Appendix, Table S9, Figure S7).

During childhood, higher levels of PM<sub>2.5</sub> were associated with higher fine motor scores in the single-exposure models (+1.0 point (95% CI 0.7, 1.9)) (Fig. 3, and Appendix, Table S8) which remained in the multi-exposure models (Table 4, and Appendix, Table S9). However, this association disappeared in the meta-analysis (+0.1 point (95% CI -1.3, 1.6)) (Table 4, and Appendix, Figure S7). We observed slight heterogeneity between areas, with a negative association observed for the EDEN-Nancy cohort (-6.2 points (95% CI -11.1, -1.3)) (Appendix, Figure S7), while no association was found for the other areas.

No associations were observed between air pollution during pregnancy and childhood and non-verbal abilities and gross motor function (Fig. 2, Fig. 3, and Appendix, Table S8).

### 3.4. Mediation between urban environment, air pollution exposure, and cognitive and motor scores

Since we only found that two urban environment indicators during childhood (i.e., NDVI in 300 m buffer and land use diversity) and exposure to PM<sub>2.5</sub> during childhood were associated with verbal abilities in the BiB cohort (Appendix, Figure S6), we restricted our mediation analyses to this cohort. NDVI in 300 m buffer was associated with lower

PM<sub>2.5</sub> levels (-0.56 95% CI (-0.60, -0.52)). Land use diversity was associated with a slight increase of PM<sub>2.5</sub> levels, but the association was not statistically significant (0.01 95% CI (-0.03, 0.05)). Therefore, we conducted the mediation analysis only for NDVI. We observed that air pollution mediated 74% of the association between NDVI in 300 m buffer and verbal scores (natural indirect effect: 1.5 point (95% CI 0.6, 2.4), total effect: 2.0 points (95% CI 0.5, 3.7)) (Fig. 4).

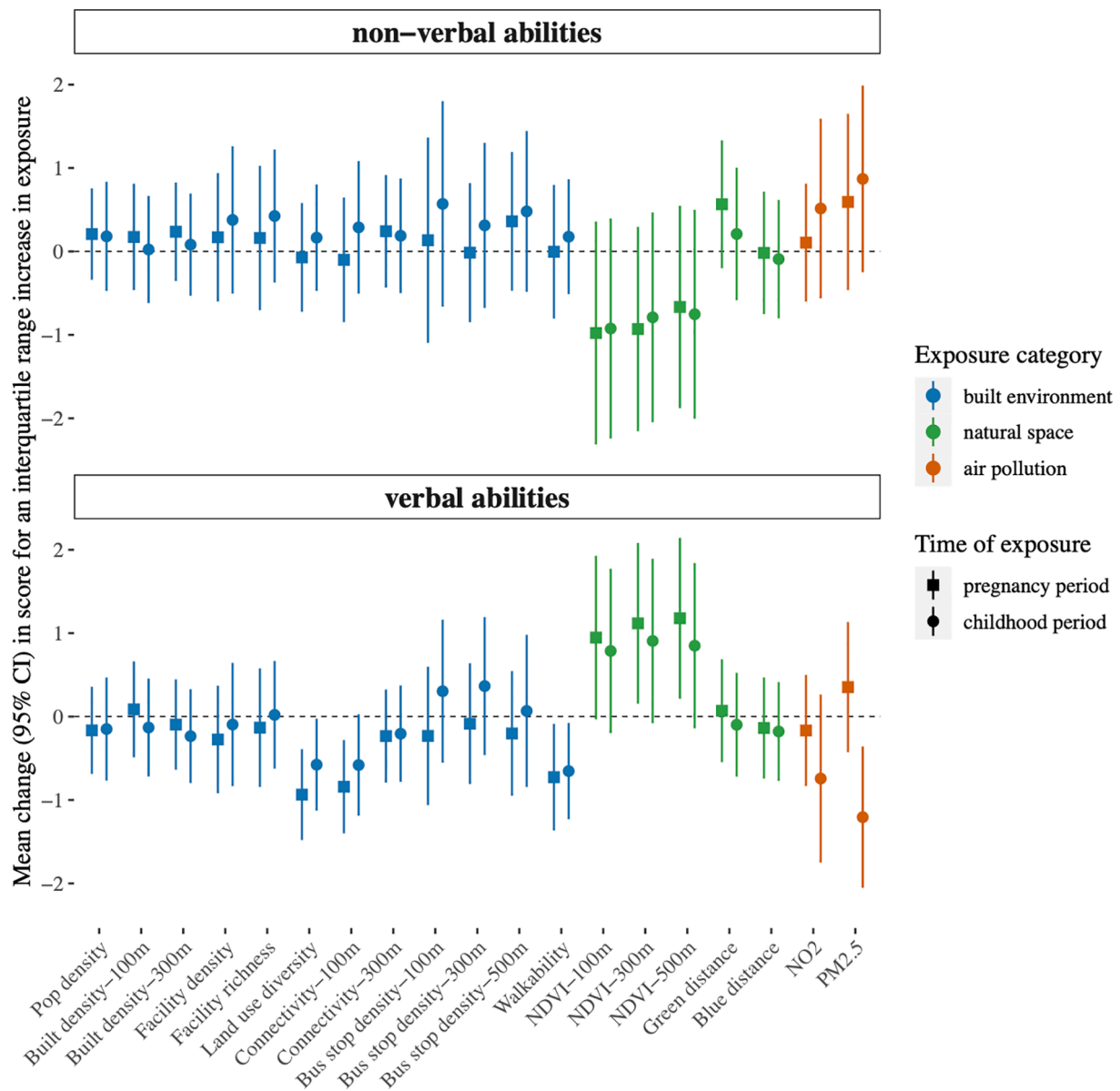
## 4. Discussion

In this large urban environment study, we observed that higher exposure to PM<sub>2.5</sub> during pregnancy was associated with lower fine motor function. Also, higher street connectivity during pregnancy, and land use diversity during both pregnancy and childhood were associated with lower verbal abilities, and higher surrounding greenness during pregnancy was associated with higher verbal abilities. In analyses restricted to one cohort, childhood exposure to PM<sub>2.5</sub> mediated almost 75% of the association of surrounding greenness during childhood, with verbal abilities.

Several studies have reported negative associations between air pollution and motor development in children, though some have also reported null effects (Guxens et al., 2014; Lertxundi et al., 2019; Lubczyńska et al., 2017; Zhang et al., 2020). In line with existing studies, we observed that higher PM<sub>2.5</sub> levels during pregnancy were associated with lower fine motor scores. In particular, we found consistent results with a previous study that included some of the birth cohorts of our study at a younger age (EDEN, INMA, and RHEA) (Guxens et al., 2014). During pregnancy, the placenta and the blood–brain barriers are still immature defense systems and grant only partial protection to the fetus against environmental pollutants (Block et al., 2012). Fine particles may deposit in the respiratory tract of pregnant women and soluble components translocate into the circulation, generating systemic inflammation (US EPA, 2016). Both systemic inflammation and translocation of the air pollutants might directly affect fetal development by impairing placental function, decreasing transplacental oxygen and nutrient transport, and producing placental oxidative stress and epigenetics changes (Block et al., 2012).

Growing evidence suggests that exposure to greenness is beneficial for cognitive abilities in children (Asta et al., 2020; Davdand et al., 2015; Liao et al., 2019). Our results suggest that the positive effect of surrounding greenness on verbal abilities was mostly mediated by a reduction of air pollution levels, in line with previous findings in the literature (Asta et al., 2020; Davdand et al., 2015; Liao et al., 2019; Markevych et al., 2017; Nieuwenhuijsen et al., 2017). For example, a study observed that 20 to 65% of the associations between school greenness and working memory at seven- to ten-year-old were mediated by elemental carbon exposure (Dadvand et al., 2015). In another study, prenatal exposure to PM<sub>2.5</sub> mediated about 11% of the association between residential exposure to greenness and mental development at twenty-four-month-old (Liao et al., 2019). Similarly, NO<sub>2</sub> exposure mediated 35% of the association between residential exposure to greenness and arithmetic abilities at 7-year-old (Asta et al., 2020). Higher physical activity and frequency of social contacts may be also mediators of the effect of green spaces on human health (Nieuwenhuijsen et al., 2017). Other possible mechanisms of the effects of green spaces on cognitive function include stress reduction and restoration (Nieuwenhuijsen et al., 2017). The Stress Reduction theory proposes psychophysiological pathways to explain the recovery from stress when exposed to nature, including positive changes in emotional state and physiological activity levels, and sustained attention/intake (Ulrich et al., 1991). Kaplan (1995) suggests in the Attention Restoration Theory how nature could act as a restorative environment for reducing fatigue of directed attention. Future studies should investigate the relationship between urban environment and allostatic load score in humans.

This is the first study, to our knowledge, that showed a negative association between some built environment indicators (i.e., street



**Fig. 2. Single-exposure adjusted associations between urban environment during pregnancy and childhood and cognitive function (N = 5,363 for verbal abilities, N = 3,306 for non-verbal abilities).** CI, Confidence interval; NDVI, Normalized Difference Vegetation Index; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter of less than 2.5 μm; Pop, Population. Estimates are expressed as mean change for an interquartile range increase of exposure. Adjusted for area of inclusion, deprivation index at area level, season of birth, native parents of the country of recruitment, maternal and paternal age at recruitment, maternal smoking during pregnancy, maternal pre-pregnancy body mass index, paternal body mass index at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment.

connectivity density and land use diversity) and verbal abilities. Even if previous studies demonstrated that greenness is an important factor in the urban environment for human health (WHO Regional Office for Europe, 2016), in our study two other urban environment factors, connectivity density and land use diversity remained associated with lower verbal abilities after adjusting for greenness. Thus, our findings suggest that other urban characteristics beyond green spaces are important factors to consider when studying environmental exposures that may have an impact on children’s cognition. No published studies, to our knowledge, have investigated the effects of built design on cognitive development in children (Gascon et al., 2016). To date, most epidemiological studies about child development have considered individual family, and school environments, but little the neighborhood context. It may be difficult to disentangle the effects of built environment from socioeconomic status, as people from lower economic status are more

likely to live in deprived neighborhood (Villanueva et al., 2016). Nevertheless, neighborhood may affect child’s development through social interaction and time spent outdoor. Neighborhood safety concerns may influence family practices. Low-density suburban neighborhood may be associated with desirable features (e.g., low crime, low noise and traffic) but less walkable areas and higher distances to essential services. This results in more time commuting and less time exploring and interacting with people and their environment, and may potentially negatively affect child health and development (Besser et al., 2017; Robinson et al., 2018; Villanueva et al., 2016). Further investigations are warranted to replicate our results and to better understand the effects of built design on child cognitive abilities.

In the present study, we found no evidence of an association of built environment, green space, and air pollution indicators, either during pregnancy or childhood, with non-verbal abilities and gross motor

**Table 4**

Multi-exposure adjusted association between pregnancy and childhood urban exposures and verbal abilities (N = 5,363) and fine motor function (N = 5,228).

		<u>Pregnancy period</u>		<u>Childhood period</u>	
		<u>Mega-analysis</u>	<u>Meta-analysis</u>	<u>Mega-analysis</u>	<u>Meta-analysis</u>
		Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
<b>Verbal abilities</b>					
Urban environment	Connectivity density in 100 m buffer ( $\Delta$ 192.2 intersections/km <sup>2</sup> )	-0.8 (-1.4, -0.2)	-0.8 (-1.4, -0.1)	..	..
	Land use diversity ( $\Delta$ 0.1 units)	-0.9 (-1.4, -0.3)	-0.8 (-1.4, -0.3)	-0.6 (-1.1, 0.0)	-0.3 (-1.1, 0.4)
	NDVI in 500 m buffer ( $\Delta$ 0.2 units)	1.5 (0.4, 2.7)	1.6 (-0.1, 3.4)	..	..
	Building density in 100 m buffer ( $\Delta$ 131,637 m <sup>2</sup> /km <sup>2</sup> )	0.8 (0.1, 1.5)	0.6 (-0.2, 1.4)	..	..
Air pollution	PM2.5 ( $\Delta$ 3.2 $\mu$ g/m <sup>3</sup> )	..	..	-1.2 (-2.1, -0.4)	0.0 (-1.7, 1.6)
<b>Fine motor function</b>					
Air pollution	PM2.5 ( $\Delta$ 3.2 $\mu$ g/m <sup>3</sup> )	-1.2 (-2.1, -0.4)	-0.9 (-2.2, 0.4)	1.0 (0.1, 1.9)	0.1 (-1.3, 1.6)

CI, confidence interval; NDVI, Normalized Difference Vegetation Index; PM2.5, particulate matter with an aerodynamic diameter of less than 2.5  $\mu$ m. The selection of exposures was determined by backward selection following the DSA (Deletion-Substitution-Addition) algorithm. DSA selections were performed separately for the prenatal and the childhood exposome, for urban environment and air pollution indicators, and for verbal abilities and fine motor function. Estimates are expressed as mean change for an interquartile range increase of exposure. Estimates adjusted for co-exposures (urban environment or air pollution), area of inclusion, deprivation index at area level, season of birth, native parents of the country of recruitment, maternal and paternal age at recruitment, maternal smoking during pregnancy, maternal pre-pregnancy body mass index, paternal body mass index at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment.

function. Previous studies on non-verbal abilities reported mostly null associations with early-life exposure to greenness and air pollution (Asta et al., 2020; Guxens et al., 2014; Lertxundi et al., 2019). Findings about gross motor function are more inconsistent: some studies have reported positive associations with early-life exposure to greenness and negative associations with air pollution exposure, but some studies found no association with air pollution (Guxens et al., 2014; Kabisch et al., 2019; Lertxundi et al., 2019; Liao et al., 2019; Lubczyńska et al., 2017). Non-verbal abilities and gross motor function were not assessed in some cohorts of our study, resulting in smaller sample sizes. We cannot discard the possibility that we lacked statistical power to find an association with these two outcomes.

The main strengths of this study include: i) its prospective multi-centric design with seven urban areas from four European countries, ii) the large range of urban factors evaluated at different time points from the prenatal period onwards with standardized and validated assessment methods, iii) the use of validated neuropsychological tests performed at homogeneous ages, iv) the simultaneous evaluation of multiple groups of exposures of the urban environment, v) the mediation analysis to disentangle the role of the urban environment and air pollution, and vi) the adjustment for various socioeconomic and lifestyle variables known to be potentially associated with the urban environment during early-life and with cognitive and motor function in children.

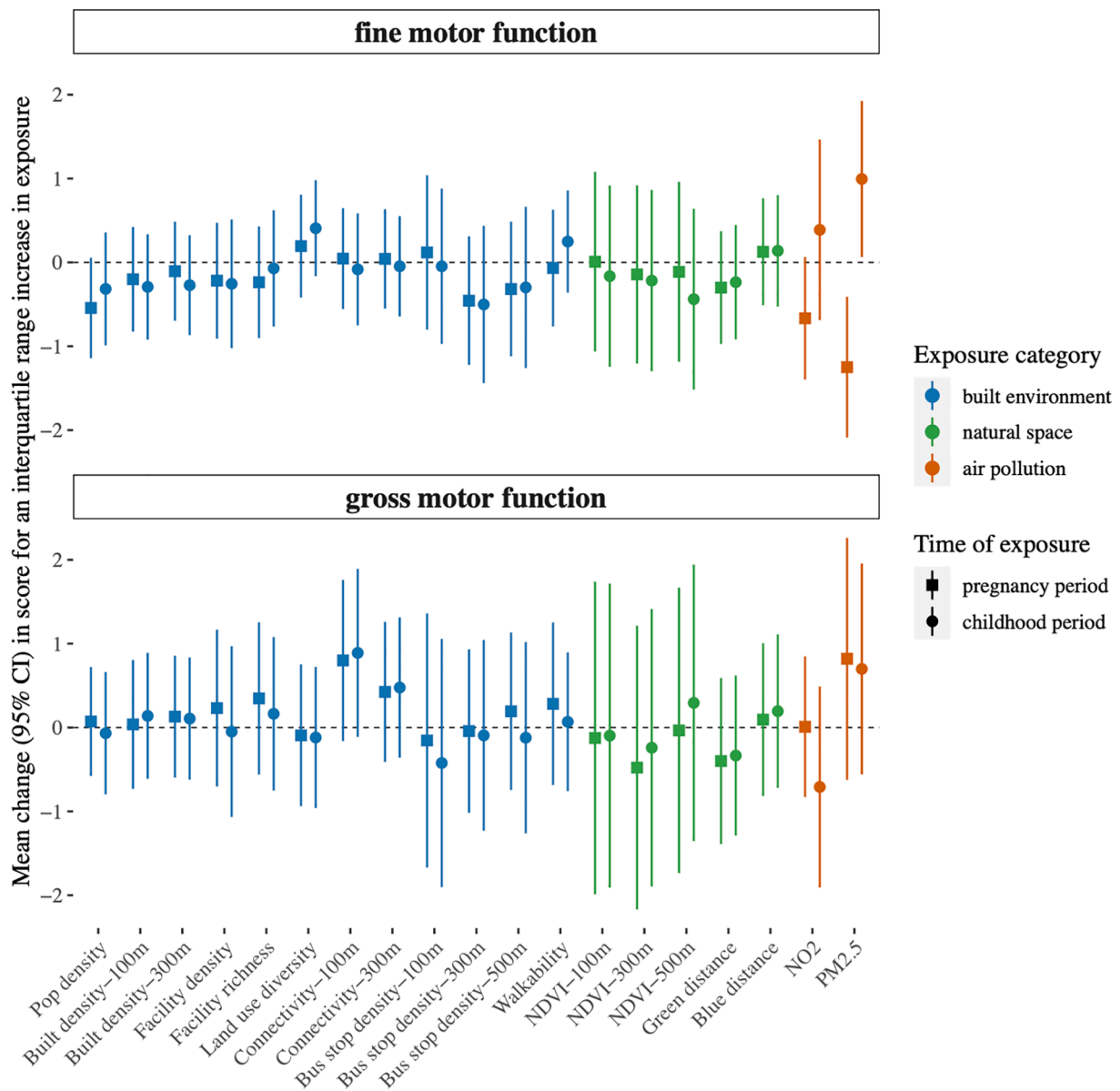
However, we acknowledge that this study has several limitations. First, the neuropsychological tests used differed across cohorts, due to the use of already collected data, which is likely to have introduced between-cohort heterogeneity. We have included tests assessing the same cognitive and motor functions to minimize that limitation, although moderate correlations between some tests might have introduced noise and decreased our chance to detect associations (Karr et al., 1993). Second, while it is important to consider the entire urban environment, our analysis has methodological limits. Single-exposure associations should be interpreted with caution because they can be affected by type I error. Therefore, we applied a multi-exposure modeling, the DSA algorithm, to correct for multiple testing which takes into account the correlation between co-exposures. However, it has been previously shown that when two correlated variables are considered as predictors in a regression model, the variable estimated with less measurement error is selected even if the other variable is the one causally related to the outcome. Furthermore, the DSA algorithm is based on a cross-validation process which is subject to random variations. We ran each model 200 times and selected final models that occurred in at least 10% of the run. However, these results might not be completely robust and stable, and the percentage of times the variables were selected should be

considered when interpreting the results. We were also not able to mutually adjust for prenatal and childhood exposure due to high correlation between the two periods. Third, the exposure assessment has limitations too. Air pollution was modeled to the individual level of home addresses of each participant using land use regression models based on validated measurements. However, a source of misclassification emerges when a participant spends time away from home (e.g., at work during pregnancy or at day care during early-childhood). Information about addresses where participants spent most of their time and commuting routes (in particular in the time of the day when air pollution levels are higher) is crucial for estimating total outdoor air pollution exposure. Our findings could be affected by non-differential misclassification, resulting in a possible underestimation of the true association (Pollack et al., 2013). Fourth, participants of the study had a higher socio-economic status than non-participants, leading to potential selection bias. This selection bias due to attrition prevent us to generalize the results. Fifth, we cannot exclude residual confounding. Despite the wide range of exposures, we investigated, we may have missed some unmeasured urban environmental factors or confounding and mediating factors. In particular, we considered noise and heat exposure but were unable to include these due to poor or lack of measurement (e.g., noise assessments were available for only 52% of the children). In a previous HELIX study (Robinson et al., 2018), built environment and natural spaces indicators have been correlated with noise levels. It is likely that noise, such as air pollution, may be a mediator in the association between urban environment and cognition and motor function. Further studies should consider noise when studying urban environmental factors. Also, we missed information about parental mental health and intelligence status. Residual confounding could lead to biased estimates of the associations (Weisskopf et al., 2018).

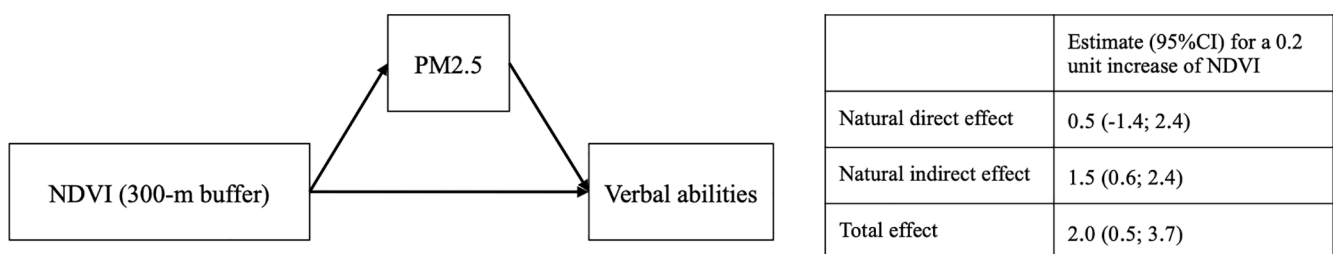
## 5. Conclusion

This study highlights that early-life urban environment, in particular during pregnancy, may have adverse effects on cognitive and motor function in children. Specifically, early-life exposure to some built environment design factors, greenness, and air pollution were related to small alterations of child cognitive and motor function at five years old. The work has confirmed possible mediation effects by air pollution of the association between green space and verbal abilities. Most interestingly, the present study has provided new insights into the negative association of built environment indicators and cognitive function. This study adds evidence that well-designed urban planning may promote children's cognitive and motor function.





**Fig. 3. Single-exposure adjusted associations between urban environment during pregnancy and childhood and motor function (N = 5,228 for fine motor, N = 2,199 for gross motor).** CI, Confidence interval; NDVI, Normalized Difference Vegetation Index; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter of less than 2.5 μm; Pop, Population. Estimates are expressed as mean change for an interquartile range increase of exposure. Adjusted for area of inclusion, deprivation index at area level, season of birth, native parents of the country of recruitment, maternal and paternal age at recruitment, maternal smoking during pregnancy, maternal pre-pregnancy body mass index, paternal body mass index at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment.



**Fig. 4. Mediation analyses between urban environment during childhood, air pollution exposure during childhood, and verbal scores at five-year-old in the BiB cohort (N = 2,057).** CI, Confidence interval; NDVI, Normalized Difference Vegetation Index; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter of less than 2.5 μm. Estimates are expressed as mean change for an interquartile range increase of exposure. Adjusted for deprivation index at area level, season of birth, native parents of the country of recruitment, maternal and paternal age at recruitment, maternal smoking during pregnancy, maternal pre-pregnancy body mass index, paternal body mass index at recruitment, parity, maternal and paternal educational levels, child sex, and child age at assessment.

## CRedit authorship contribution statement

**Anne-Claire Binter:** Writing - original draft, Formal analysis, Investigation. **Jonathan Y. Bernard:** Resources, Writing - review & editing. **Mark Mon-Williams:** Resources, Writing - review & editing. **Ainara Andiarena:** Resources, Writing - review & editing. **Llúcia González-Safont:** Resources, Writing - review & editing. **Marina Vafeiadi:** Resources, Writing - review & editing. **Johanna Lepeule:** Resources, Writing - review & editing. **Raquel Soler-Blasco:** Resources, Writing - review & editing. **Lucia Alonso:** Data curation, Writing - review & editing. **Mariza Kampouri:** Resources, Writing - review & editing. **Rosie Mceachan:** Resources, Writing - review & editing. **Loreto Santa-Marina:** Resources, Writing - review & editing. **John Wright:** Resources, Writing - review & editing. **Leda Chatzi:** Resources, Writing - review & editing. **Jordi Sunyer:** Resources, Writing - review & editing. **Claire Philippat:** Resources, Writing - review & editing. **Mark Nieuwenhuijsen:** Methodology, Writing - review & editing. **Martine Vrijheid:** Funding acquisition, Writing - review & editing. **Mònica Guxens:** Conceptualization, Supervision, Writing - review & editing.

## 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.

## Acknowledgements

We are grateful to all the participating children, parents, practitioners and researchers in the four countries who took part in this study. This work was supported by funding from the European Community's Seventh Framework Programme [FP7/2007–2013 n. 308333; the HELIX project]. This INMA cohort was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds, FIS PI06/0867, FIS-PI09/00090, FIS and FIS-PI18/01142 incl. FEDER funds, FIS-FEDER: PI03/1615, PI04/1509, PI04/1112, PI04/1931, PI05/1079, PI05/1052, PI06/1213, PI07/0314, PI09/02647, PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI14/00891, PI14/01687, PI16/1288, PI16/00118 and PI17/00663; FIS-FSE: 17/00260; Miguel Servet-FEDER CP11/00178, CP15/00025, CP116/00051, and CP118/00018), from UE (FP7-ENV-2011 cod 282957, HEALTH.2010.2.4.5-1, and H2020 n. 824989), Generalitat de Catalunya-CIRIT 1999SGR 00241, Fundació La marató de TV3 (090430), Generalitat Valenciana: FISABIO (UGP 15-230, UGP-15-244, and UGP-15-249), Alicia Koplowitz Foundation 2017, CIBERESP, Department of Health of the Basque Government (2013111089, 2009111069, 2013111089, 2015111065 and 2018111086), Provincial Government of Gipuzkoa (DFG06/002, DFG08/001, DFG15/221 and DFG 89/17) and annual agreements with the municipalities of the study area (Zumarraga, Urretxu, Legazpi, Azkoitia y Azpeitia y Beasain). We acknowledge support from the Spanish Ministry of Science and Innovation and the State Research Agency through the “Centro de Excelencia Severo Ochoa 2019-2023” Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program. The work was also supported by MICINN [MTM2015-68140-R] and Centro Nacional de Genotipado-CEGEN-PRB2-ISCI (Spain). The Rhea project was financially supported by European projects, and the Greek Ministry of Health (Program of Prevention of obesity and neurodevelopmental disorders in preschool children, in Heraklion district, Crete, Greece: 2011–2014; “Rhea Plus”: Primary Prevention Program of Environmental Risk Factors for Reproductive Health, and Child Health: 2012–15). This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Collaboration for Applied Health Research and Care (CLAHRC) for Yorkshire and Humber (UK). The EDEN study was supported by Foundation for medical research (FRM), National Agency for Research (ANR), National Institute for Research in

Public health (IRESP: TGIR cohorte santé 2008 program), French Ministry of Health (DGS), French Ministry of Research, INSERM Bone and Joint Diseases National Research (PRO-A), and Human Nutrition National Research Programs, Paris-Sud University, Nestlé, French National Institute for Population Health Surveillance (InVS), French National Institute for Health Education (INPES), the European Union FP7 programs (ESCAPE, ENRIECO, Medall projects), Diabetes National Research Program (through a collaboration with the French Association of Diabetic Patients (AFD)), French Agency for Environmental Health Safety and French National Agency for Food Security (now ANSES), Mutuelle Générale de l'Éducation Nationale a complementary health insurance (MGEN), French-speaking association for the study of diabetes and metabolism (ALFEDIAM). Core support for Born in Bradford is also provided by the Wellcome Trust (WT101597MA, UK). Born in Bradford (BiB) is only possible because of the enthusiasm and commitment of the children and parents in BiB. We are grateful to all the participants, health professionals, schools and researchers who have made BiB happen. BiB receives funding from the ESRC/MRC, the Wellcome Trust (WT101597MA) and the National Institute for Health Research Yorkshire and Humber ARC (reference: NIHR20016). M. Mon-Williams was supported by a Fellowship from the Alan Turing Institute. Additional funding from the National Institute of Environmental Health Science supported Dr Chatzi (R01ES030691, R01ES029944, R01ES030364, R21ES029681, and P30ES007048). The views expressed are those of the authors, and not necessarily those of the NHS or the NIHR. None of the funders were involved in designing the study, collecting the data, analyzing or interpreting the data, deciding to submit the article for publication, or the writing of the report.

## Data sharing statement

The HELIX data warehouse has been established as an accessible resource for collaborative research involving researchers external to the project. Access to HELIX data is based on approval by the HELIX Project Executive Committee and by the individual cohorts. Further details on the content of the data warehouse (data catalogue) and procedures for external access are described on the project website (<http://www.projecthelix.eu/index.php/es/data-inventory>).

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2021.106933>.

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