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Urban environment during early-life and blood pressure in young children

Charline Warembourg [a,b,c,*], Mark Nieuwenhuijsen [a,b,c], Ferran Ballester [c,d,e], Montserrat de Castro [a,b,c], Leda Chatzi [f], Ana Esplugues [c,d,e], Barbara Heude [g], Léa Maitre [a,b,c], Rosemary McEachan [h], Oliver Robinson [i], Rémy Slama [j], Jordi Sunyer [a,b,c], Jose Urquiza [a,b,c], John Wright [h], Xavier Basagaña [a,b,c], Martine Vrijheid [a,b,c]

[a] ISGlobal, Doctor Aiguader 88, 08003 Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[d] Department of Nursing, Universitat de València, Valencia, Spain
[e] FISABIO-Universitat Jaume I-Universitat de València Joint Research Unit of Epidemiology and Environmental Health, Valencia, Spain
[f] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[g] Université de Paris, Center for Research in Epidemiology and StatisticS (CRESS), INSERM, INRA, F-75004 Paris, France
[h] Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
[i] MRC Centre for Environment and Health, School of Public Health, Imperial College London, UK
[j] Inserm, Univ. Grenoble Alpes, CNRS, IAB (Institute of Advanced Biosciences), Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, Grenoble, France

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ABSTRACT

Background: The urban environment is characterised by many exposures that may influence hypertension development from early life onwards, but there is no systematic evaluation of their impact on child blood pressure (BP).

Methods: Systolic and diastolic blood pressure were measured in 4,279 children aged 4–5 years from a multicentre European cohort (France, Greece, Spain, and UK). Urban environment exposures were estimated during pregnancy and childhood, including air pollution, built environment, natural spaces, traffic, noise, meteorology, and socioeconomic deprivation index. Single- and multiple-exposure linear regression models and a cluster analysis were carried out.

Results: In multiple exposure models, higher child BP, in particular diastolic BP, was observed in association with higher exposure to air pollution, noise and ambient temperature during pregnancy, and with higher exposure to air pollution and higher building density during childhood (e.g., mean change [95% confidence interval] for an interquartile range increase in prenatal NO_2 = 0.7 mmHg[0.3;1.2]). Lower BP was observed in association with higher temperature and better street connectivity during childhood (e.g., temperature = -1.1[-1.6;-0.6]). Some of these associations were not robust in the sensitivity analyses. Mother-child pairs were grouped into six urban environment exposure clusters. Compared to the cluster representing the least harmful urban environment, the two clusters representing the most harmful environment (high in air pollution, traffic, noise, and low in green space) were both associated with higher diastolic BP (1.3[0.1;2.6] and 1.5[0.5;2.5]).

Conclusion: This first large systematic study suggests that living in a harmful urban environment may impact BP regulation in children. These findings reinforce the importance of designing cities that promote healthy environments to reduce long-term risk of hypertension and other cardiovascular diseases.

1. Introduction

Hypertension is one of the main risk factors of cardiovascular diseases, but its aetiology is complex and multifactorial as it can be the result of an interplay between genetic, lifestyle, and environmental risk factors [1,2]. Longitudinal studies of blood pressure have found that children with elevated blood pressure are more likely to develop hypertension in adulthood [3]. Together with the growing evidence about

* Corresponding author at: Barcelona Institute for Global Health (ISGlobal), Doctor Aiguader, 88, 08003 Barcelona, Spain.
E-mail address: charline.warembourg@isglobal.org (C. Warembourg).

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the fetal origins of hypertension [4,5], this highlights the importance of identifying environmental risk factors contributing to hypertension development early in life, from the fetal period onwards.

With the worldwide growth in urbanization, there are growing concerns about the impact of urban design and transport planning on environment and human health [6]. It is now well established that exposure to air pollution can increase blood pressure and is a major contributor of cardiovascular disease in adulthood: according to the Global Burden of Disease (2016), 19% of all cardiovascular deaths are attributed to air pollution [1,7]. Several studies in adults have reported that other exposures in the urban environment such as noise and lack of green spaces may contribute to a higher risk of hypertension and other cardiovascular diseases [8–10]. Further, ambient temperature is also known to affect blood pressure, with cold temperature leading to the narrowing of blood vessels which in turn leads to a rise in blood pressure [11]. Although limited in number, some studies reported that built environment features (e.g., high building density, poor walkability) were associated with higher blood pressure [9].

In children, knowledge on how the urban environment may affect blood pressure is mainly based on cross-sectional studies showing higher blood pressure in children exposed to higher exposure to air pollution [12], cold temperature [13,14], lack of green spaces [15,16], and less consistently to higher exposure to noise [8,17]. Longitudinal studies covering the prenatal and early postnatal period are scarce but have shown higher blood pressure in newborns and children aged 3 to 12 years old with higher air pollution exposure during pregnancy [18–21]. Results on noise exposure during early life are not consistent and studies on the effect of other built environment features, either during pregnancy or childhood, are lacking [22].

With a few exceptions [14,15], studies have evaluated health risks related to single urban exposures, thus not accounting for the complex correlations that exist between exposures [23]. A more holistic view of the urban environment, evaluating many exposures related to urbanisation simultaneously, may be valuable to disentangle the independent or confounded effects of various exposures and to identify the strongest determinants of cardiovascular health.

This study systematically assesses the association between multiple urban exposures, measured pre and postnatally, and blood pressure in preschool children from a large multi-centre European cohort.

2. Methods

2.1. Study population

This study is based on the Human Early-life Exposome project (HELIX), a European consortium of six existing birth cohorts, described elsewhere [24]. Briefly, pregnant women were recruited between 1999 and 2010, in medical settings during the first or the second trimester of pregnancy when attending for routine care examination. Each cohort had at least one follow-up point during pregnancy, one at birth, and several after birth. Mother-child pairs with available data on blood pressure in children at age 4 to 5 years old were included in the present study restricting the study population to 4 of the 6 cohorts, and corresponding to 6 cities: BIB (*Born in Bradford*) in Bradford (UK) [25], EDEN (*Étude des Déterminants pré et postnatals du développement et de la santé de l'Enfant*) in Poitiers and Nancy (France) [26], INMA (*Infancia y Medio Ambiente*) in Sabadell and Valencia (Spain) [27], and RHEA (*Mother Child Cohort study in Crete*) in Heraklion (Greece) [28]. In these 4 cohorts, 31% (n = 4,970) children had available data on BP measurements (Appendix Figure A1). Each cohort has obtained approval from the national ethics committees and all participating women have provided informed written consent.

2.2. Blood pressure assessment

Systolic (SBP) and diastolic (DBP) blood pressure were measured during a clinical visit performed at age 4 to 5 years. Blood pressure assessment was specific to each cohort in terms of number of readings and device used; details are provided in Appendix Table A1. A single reading was taken in BIB and INMA-Sabadell, at least 2 in INMA-Valencia, 3 in EDEN, and 5 in RHEA. In order to limit differential measurement error by cohort, the first reading was retained in the primary analysis; the average of all available readings were used in a sensitive analysis. Age-, sex- and height-specific z-score of SBP and DBP were calculated using existing charts [29]. Missing height led to the exclusion of 437 (9%) children. Children with SBP or DBP z-score higher or lower than to 3 standard deviation were additionally excluded (n = 254, 5%) to limit the influence of extreme value and measurement errors. Raw blood pressure values were used as a primary analysis. The final study population included 4,279 children (Appendix Figure A1).

2.3. Assessment of the urban environment during early-life

The urban environment was assessed using GIS-based modelling according to the residential address of the mothers during pregnancy (from conception to birth) and at the time of the 4–5 years old visit. Several components of the urban environment were assessed including built environment, natural spaces, traffic, air pollution, noise, meteorology, and socioeconomic deprivation index (Table 1). Exposure assessment for these exposure groups was conducted within the PostgreSQL, PostGIS, and QGIS platforms. The source of data and the assessment methods used for each exposure are fully described in Appendix B. Time-varying exposures including air pollution and meteorology were averaged within different intervals: the whole pregnancy, the 1st, 2nd, and 3rd trimesters of pregnancy, the first year of life, and the year, the month, the week, or the day before the measurement of blood pressure. The built environment and natural spaces were measured within different buffers: 100 m, 300 m, or 500 m.

2.4. Data pre-processing

Exposures not assessed in>3 of the 6 cities, or exposures with>70% of missing overall, were excluded. These included straight line distance to closest street (pregnancy and childhood) and PM absorbance (childhood). Further, we excluded pressure (pregnancy and childhood) and humidity (pregnancy) variables as their distributions were totally cohort-dependent (i.e. they showed no overlap across cohorts). Then, a selection was performed to avoid correlations > 0.9 between the remaining variables, leading to the exclusion of 2 of the 3 indices of UV exposures (i.e., Erythemal UV dose and Vitamine-D UV dose). This pre-selection reduced from 157 to 125 the number of exposures included in the present study. Variable transformations were applied to reach normality (otherwise variables were categorized) before imputing missing data using chained equations [30]. Five imputed datasets were generated and Rubin's rules were applied to summarize effect estimates [30].

2.5. Statistical analysis

Three complementary approaches were used to (1) describe single-exposure associations, (2) develop a multi-exposure model to obtain adjusted associations, and (3) identify subgroups of children sharing similar urban exposure patterns. First, we performed an Exposure-wide association study (ExWAS) using multiple linear regression models to study the association of each exposures independently (60 during pregnancy, 5 during the first year of life, and 60 at 4–5 years old) and accounting for multiple testing using a Bonferroni-type correction [31]. Then, we applied a variable selection method using the Deletion-Substitution-Addition (DSA) algorithm to identify prenatal and postnatal exposures jointly associated with blood pressure. This was considered as the main statistical analysis and resulted in our final multi-exposure models. This method was selected for its lower false discovery rate along with reasonable sensitivity according to a simulation study

Table 1
Exposures considered in the urban environment.

	Pregnancy	Childhood (4–5 years old)*
Air pollution	$PM_{2.5}$ (pregnancy†, T1, T2, T3)	$PM_{2.5}$ (the year†, the month, the week, and the day† before the BP measurement)
	$PM_{absorbance}$ (pregnancy†, T1, T2, T3)	PM_{coarse} (year†, month, week, day†)
	PM_{10} (pregnancy†, T1, T2, T3)	PM_{10} (year, month, week, day)
	NO_2 (pregnancy†, T1, T2, T3)	NO_2 (year†, month, week, day†)
	NO_X (pregnancy, T1, T2, T3)	NO_x (year, month, week, day)
Built environment	Length of public transport lines (100 m, 300 m†, 500 m)	Length of public transport lines (100 m, 300 m†, 500 m)
	Density of public bus stops (100 m, 300 m†, 500 m)	Density of public bus stops (100 m, 300 m†, 500 m)
	Building density (100 m, 300 m†)	Building density (100 m, 300 m†)
	Connectivity density (100 m, 300 m†)	Connectivity density (100 m, 300 m†)
	Facility density (300 m) †	Facility density (300 m) †
	Facility richness (300 m)	Facility richness (300 m)
	Land use Shannon's Evenness Index (300 m) †	Land use Shannon's Evenness Index (300 m) †
	Population density†	Population density†
	Walkability index (mean†, sum)	Walkability index (mean†, sum)
Meteorological conditions	Temperature (pregnancy†, T1, T2, T3)	Temperature (month, week, day†)
	UV index (pregnancy, T1, T2, T3)	UV index (month, week, day)
	–	Humidity (month, week, day†)
Natural spaces	Presence of major green space (300 m)‡	Presence of major green space (300 m)‡
	Distance to nearest major green space†	Distance to nearest major green space†
	Size of nearest major green space†	Size of nearest major green space†
	NDVI (100 m, 300 m, 500 m†)	NDVI (100 m, 300 m, 500 m†)
	Presence of major blue space (300 m)‡	Presence of major blue space (300 m)‡
	Distance to nearest major blue space†	Distance to nearest major blue space†
	Size of nearest major blue space†	Size of nearest major blue space†
Traffic	Inverse distance to nearest road†	Inverse distance to nearest road†
	Traffic load on all roads in 100 m buffer†	Traffic load on all roads in 100 m buffer†
	Traffic density in nearest road†	Traffic density in nearest road†
	Presence of major road (100 m)‡	Presence of major road (100 m)‡
Noise	Traffic noise (lden, 24 h) †	Traffic noise (lden, 24 h) †
	Traffic noise at night (ln, night) †	Traffic noise at night (ln, night) †
Socio-economic area	Deprivation index at area-level†	Deprivation index at area-level†

Lden, Day-evening-night noise level; Ln, night noise level; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of less than 10 μm; PM_{abs}, absorbance of $PM_{2.5}$ filters; PM_{coarse}, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; Preg., average of the whole pregnancy; T1, average of the 1st trimester of pregnancy; T2, average of the 2nd trimester of pregnancy; T3, average of the 3rd trimester of pregnancy; UV, Ultraviolet radiation.

* Exposure to air pollution were also assessed during the first year of life of the children (yearly average) and included in the postnatal analyses.

‡ Exposures considered as candidates for the DSA selection but not included in the clustering analysis (categorical variables).

† Exposures considered as candidates for the DSA selection and included in the clustering analysis.

[32]. Candidate exposures were limited to exposures not correlated at >0.8 (which mainly occurred between exposures measured at different time points or within different buffer size, and between some exposures from a similar domain such as NO_2 and NO_x or Temperature and UV index) and retained according to the lower missing rate, i.e., 27 prenatal and 30 postnatal exposures (Table 1). DSA relies on random cross-validation, it was run 50 times to stabilize the selection and exposures that were selected in at least 5% of them were included in a multi-exposure linear regression model. Collinearity between exposures introduced in the multi-exposure model was evaluated using Variance inflation factor (VIF) and exposures reporting a VIF > 10 were excluded. Finally, a data reduction method was used to identify clusters of children that share a similar exposure pattern: exposure levels were first centred and scaled within each city, a Principal Component Analysis (PCA) was then used to reduce the data dimension, followed by an Ascending Hierarchical Classification (AHC) - based on the first components of the PCA explaining at least 85% of the variance – to identify clusters of exposure. These clusters were finally used as the independent variable in the regression model. All estimates are reported as mean change in blood pressure, expressed in mmHG, for an interquartile range (IQR) increase in exposure level.

All the statistical analyses mentioned above were adjusted for the following potential confounding variables identified using Directed Acyclic Graph [33] (Appendix Figure C1) and included the: city of inclusion (Bradford, Poitiers, Nancy, Sabadell, Valencia, Heraklion), maternal age at inclusion (years), maternal pre-pregnancy body mass index (kg/m^2) , parity (0, 1, ≥2), native parents of the country of inclusion (both, one, none), maternal education (low, middle, high), child age (months), child sex and child height (cm). Season at the time of BP assessment and potential mediating factors (i.e., birthweight, gestational age, and child weight) were not considered in the primary analyses.

Additional information on data pre-processing and statistical analyses is provided in Appendix C.

2.6. Sensitivity analyses

Single-exposure analyses (ExWAS) were repeated by using z-score of blood pressure, and additionally adjusting postnatal models for child exposure to passive smoking and child physical activity. Meta-analyses were performed for the exposures included in the multi-exposure models by 1) stratifying the models by city and 2) stratifying the models by city and using the average of all available blood pressure readings as dependent variables. Additional adjustment for season at the time of BP assessment was taken into account in the multi-exposure models and in the regression models using the clusters as an independent variable. The mediating effects of birthweight, gestational age at birth, and child weight at 4–5 years old were evaluated.

3. Results

3.1. Study population

The study population included 4,279 children at a mean age of 4.8 years old (Table 2). Most of these children were of normal body mass index (75%) and had a mean (SD) systolic and diastolic blood pressure of 98 (10.2) mmHg and 58 (9.7) mmHg, respectively. Levels of exposure during pregnancy and childhood, together with their correlations, are

Table 2
Characteristics of the study population (n = 4,279).

	Median [Q1; Q3] or N (%)
Parental characteristics	
Cohort, city, and year of birth	
BIB, Bradford (UK, 2007–2010)	1627 (38%)
EDEN, Poitiers (France, 2003–2006)	586 (14%)
EDEN, Nancy (France, 2003–2006)	501 (12%)
INMA, Sabadell (Spain, 2004–2006)	402 (9%)
INMA, Valencia (Spain, 2004–2006)	494 (12%)
RHEA, Heraklion (Greece, 2007–2008)	669 (16%)
Maternal age (years)	29.8 [26; 33]
Maternal pre-pregnancy body mass index (kg/m^2)	24.4 [21.5; 28.3]
>18.5	151 (4%)
18.5–25	2188 (52%)
25–30	1123 (27%)
>30	744 (18%)
Maternal education level	
Low	1231 (30%)
Middle	1320 (32%)
High	1544 (38%)
Parity	
0	1856 (45%)
1	1425 (35%)
≥2	848 (21%)
Maternal exposure to tobacco smoke during pregnancy	
Not exposed	1982 (49%)
Passive smoker	1159 (29%)
Active smoker	920 (23%)
Child characteristics	
Sex	
Male	2175 (51%)
Female	2104 (49%)
Gestational age (weeks)	39.7 [38.7 ; 40.7]
Preterm birth (<37 weeks)	257 (6%)
Birth weight (g)	3260 [2960; 3570]
Age at examination (years)	4.8 [4.4; 5.5]
Height at examination (cm)	108.4 [104.6; 112.7]
Weight at examination (kg)	18.6 [16.9; 20.6]
Body mass index z-score at examination (WHO growth chart)	0.3 [-0.3; 1]
Thinness	26 (1%)
Normal	3174 (75%)
Overweight	723 (17%)
Obese	334 (8%)
Systolic blood pressure at examination (mmHg)	98 [91; 104]
Diastolic blood pressure at examination (mmHg)	58 [53; 64]
Systolic blood pressure z-score at examination	0.3 [-0.3; 0.9]
Diastolic blood pressure z-score at examination	0.4 [-0.1; 0.9]
Exposed to passive smoking	
No	1405 (63%)
Potentially	460 (21%)
Yes	349 (16%)
Participate in organized sporting activity	
No	695 (48%)
Yes	753 (52%)

described in Appendix D.

3.2. Single-exposure associations with blood pressure (ExWAS analyses)

Associations between the urban environment during pregnancy and blood pressure in children were mainly observed for DBP (Fig. 1; Appendix Table E1). An increase in DBP was observed in association with higher exposure level to air pollution, namely NO_2, NO_x and $PM_{2.5}$, in particular during the first two trimesters of pregnancy (e.g., a 9.1 μg/m^3 increase in NO_2 was associated with a 0.9 mmHg [95%CI, 0.4 to 1.3] increase in DBP). Other markers of the urban environment during pregnancy such as further distance to green spaces, higher building density, traffic load, noise, temperature and UV were associated with higher systolic or diastolic blood pressure, but were no longer statistically significant after correction for multiple testing (corrected p-value threshold for significance = 0.0018).

During childhood, meteorological factors, including higher ambient temperature and UV radiation (both highly correlated), were negatively associated with systolic and diastolic blood pressure (e.g., a 11.6 °C increase in temperature the day before BP assessment was associated with a 1.1 [-1.7; −0.6] and 1.1 [-1.6; −0.6] mmHg decrease in SBP and DBP respectively), while relative humidity was positively associated with diastolic blood pressure only (Fig. 1; Appendix Table E2). In addition, the average level of NO_2 in the week and the month preceding the blood pressure assessment, and the annual average of $PM_{2.5}$ were associated with higher DBP (i.e., beta = +1.0, +1.3, and + 1.3 mmHg respectively). Other markers of the urban environment including NO_x, PM_{10}, deprivation index, green spaces, building density, traffic load, and noise, were associated with blood pressure, but were no longer statistically significant after correction for multiple testing (corrected p-value threshold for significance = 0.0019).

3.3. Multi-exposure associations with blood pressure (DSA analyses)

From the DSA selection, 5 exposures were selected in association with SBP. 24-h noise (e.g., beta for > 70 dB *vs* > 55 dB = 1.4 [-1.1; 3.9]) and ambient temperature (1.2 [-0.0; 2.5]) during pregnancy, and building density (0.8 [0.2; 1.4]) during childhood were associated with higher SBP. Middle area-level SES category during childhood (-0.9 [-1.8; −0.0]; in comparison to the first category) and living in areas with more connectivity during childhood were associated with lower SBP (−0.5 [−1.1; 0.1]) (Table 3).

For DBP, 6 factors were selected by DSA including one (PM_{10} during pregnancy, see Appendix F) *a posteriori* excluded because of collinearity in the multi-exposure model (Table 3). Higher ambient temperature measured the day before the blood pressure assessment was associated with lower DBP (−1.1 [−1.6; −0.6]). During pregnancy, exposure to higher average temperature (0.6 [−0.6; 1.7]), NO_2 (0.7 [0.3; 1.2]) and noise (i.e., beta for 60–65 dB *vs* less than 55 dB = 0.8 [-0.0; 1.7]) were associated with higher DBP, as the average exposure to $PM_{2.5}$ the year before blood pressure assessment (0.9 [0.1; 1.8]). The association between prenatal exposure to noise and DBP did not show a clear dose–response trend across quintiles.

3.4. Cluster analysis

The cluster analysis identified 6 different patterns of the urban environment presented in Fig. 2 and compares exposure levels in each cluster to the average level in the entire study population (i.e., mean = 0). Briefly, clusters 1 and 2 identified mother–child pairs exposed to low levels of air pollution, urbanization, traffic and related-noise, and to more green spaces in both the prenatal and the childhood periods, with cluster 2 being closer to the average study population levels than cluster 1. Cluster 3 identified mother–child pairs with opposite patterns of exposure between both periods, i.e., a more urban environment during pregnancy than in childhood. Clusters 4 to 6 were characterised by above average levels of exposure in both periods: cluster 4 with exposure levels closer to the average of the study population, cluster 5 being characterized by higher air pollution, traffic, and noise exposures, and cluster 6 by higher air pollution, greater urbanisation and lack of green spaces. In overall, meteorological data did not contributed to the characterization of the clusters. In comparison to cluster 1 (*a priori* the cluster with lower harmful exposures), children included in all other clusters had a higher diastolic blood pressure, in particular those in cluster 5 (beta [95%CI] = 1.3 [0.1; 2.6]) and 6 (beta [95%CI] = 1.5 [0.5; 2.5]) (Fig. 2). Higher systolic blood pressure is also suggested for children enrolled in these two clusters (Fig. 2).

3.5. Sensitivity analyses

From the first set of sensitivity analyses, similar findings were observed using z-score of blood pressure (Appendix Table G1 and

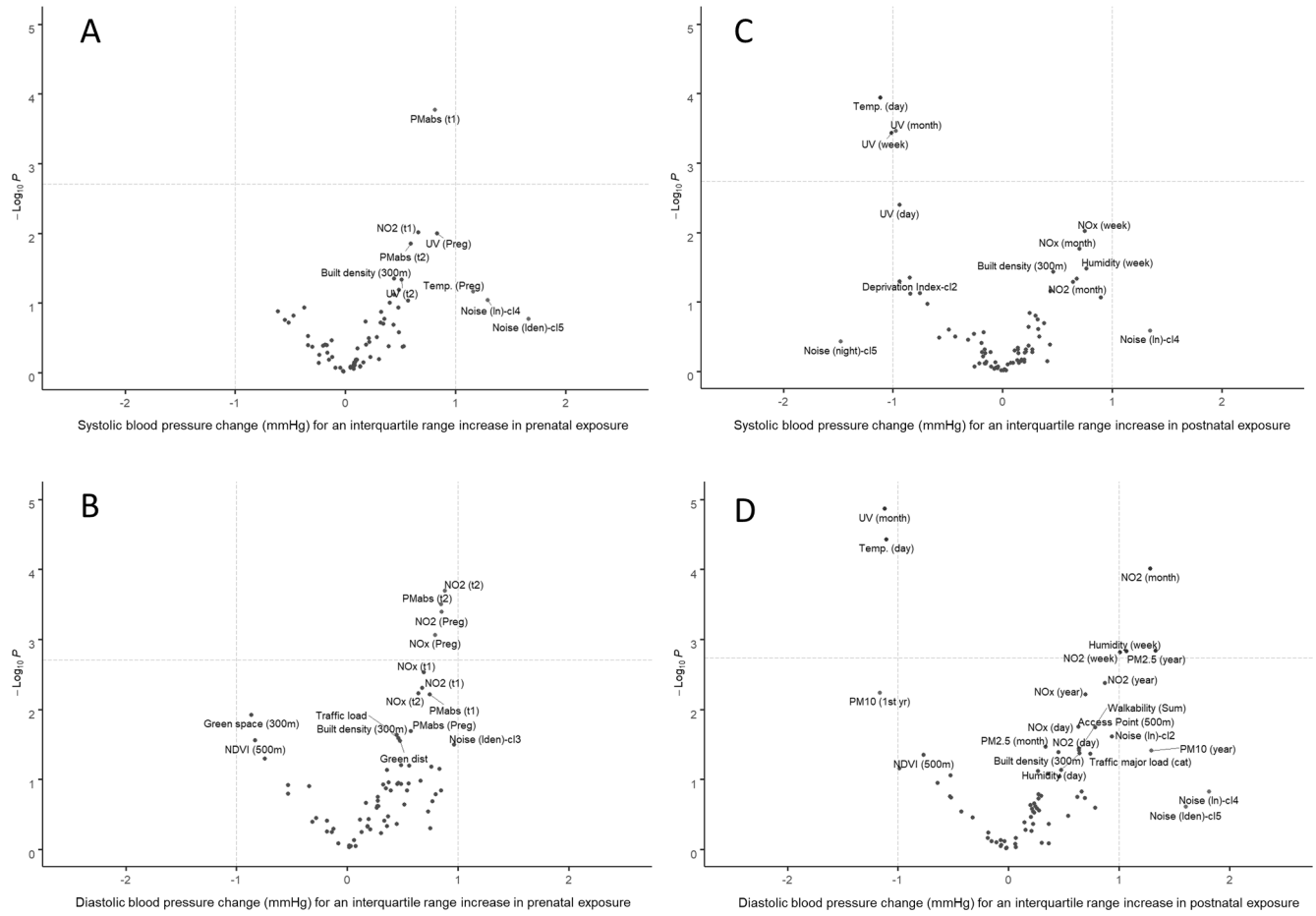

Fig. 1. Volcano plots of the Exposure Wild Association Study (ExWAS, single-exposure models) analyses between the urban environment and blood pressure at 4–5 years old (n = 4,279). Change in blood pressure is expressed in mmHG for an interquartile range increment in exposure levels. A: Prenatal exposures (n = 60) and systolic blood pressure, B: Prenatal exposures (n = 60) and diastolic blood pressure, C: Postnatal exposures (n = 65) and systolic blood pressure, D: Postnatal exposures (n = 65) and diastolic blood pressure. Estimates are adjusted for the city of inclusion (Bradford, Poitiers, Nancy, Sabadell, Valencia, and Heraklion), maternal age at inclusion (years), maternal pre-pregnancy index (kg/m^2), parity (0, 1, ≥2), native parents of the country of inclusion (both, one, none), maternal education (low, middle, high), child age (months), child sex and child height (cm). Labels are displayed for the exposures with a p-value below 0.05 or with a high effect estimate (above 1 or below −1). The horizontal dotted lines represent the p-value threshold after correction for multiple testing (i.e., p = 0.0018 for the prenatal period and p = 0.0019 for the postnatal period). Abbreviations: cl, category number; Lden, Day-evening-night noise level; Ln, night noise level; NDVI, Normalized Difference Vegetation Index; NO2, nitrogen dioxide; NOx, nitrogen oxide; PM2.5, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM10, particulate matter with an aerodynamic diameter of less than 10 μm; PMabs, absorbance of $PM_{2.5}$ filters; Preg., average of the whole pregnancy; t1, average of the 1st trimester of pregnancy; t2, average of the 2nd trimester of pregnancy; t3, average of the 3rd trimester of pregnancy; Temp, Ambient temperature; UV, Ultraviolet radiation.

Table G2) and adjusting the postnatal models for child exposure to passive smoking and child physical activity (Appendix Table G3). From the second set of sensitivity analyses, *meta*-analysis of the estimates obtained within each city provided similar conclusion as the main analysis, except for the association between ambient temperature during pregnancy and both SBP and DBP that move toward the null (Appendix Figure G1 and Figure G2). Description of outcomes, covariates, and exposure levels by city are available in Appendix Table G4. Comparing the results obtained by *meta*-analysis using the first BP reading or the average of all available readings, the estimates were similar for most exposures but weaker for prenatal and postnatal exposure to air pollution (Appendix Table G5). After adjustment for season at the time of BP assessment, the associations with postnatal temperature did not remain significant; adjustment for season has no or little impact on the other estimates (Appendix Table G6). Birthweight and gestational age at birth showed no mediation effect on the observed associations while child weight at 4–5 years old explained part (13%) of the increase in SBP observed in association with higher building density, but not with other exposures (Appendix Table G7).

4. Discussion

This first large systematic study of multiple early-life urban exposures found that living in an urban environment characterized by higher levels of air pollution, building density, and noise, and lower proximity to green spaces, during pregnancy or childhood, may contribute to an increase in blood pressure in childhood.

4.1. Air pollution

It is now well-described that exposure to air pollution is a major contributor of cardiovascular diseases and several studies have reported positive associations between air pollution and blood pressure in adults [7,34]. In children, the number of studies reporting similar findings is growing [12,19,20,35,36], but few have been able to look at both the short- and the long-term effects of air pollution [18,37,38], or covered the prenatal period [19–21]. In line with existing studies, our results report an increase in blood pressure in association with air pollution during both the prenatal and the postnatal periods. However, these associations were weaker in the sensitivity analysis performed using the

Table 3
Effect estimates of the early-life urban factors associated with blood pressure in 4–5 years old children (multi-exposure models following the DSA selection, n = 4,279).

	Interquartile range or n (%)	% of DSA selection*	Beta [95%CI]†
Systolic Blood Pressure			
Temperature (Day before BP)	11.6 °C	98	−1.1 [-1.7; −0.6]
SES-area (at 4–5 years old)		78	
1st tertile	1366 (32)		Ref.
2nd tertile	1559 (36)		−0.9 [-1.8; −0.0]
3rd tertile	1354 (32)		0.2 [-0.9; 1.2]
24-h noise (Pregnancy)		22	
<55 dB	1418 (33)		Ref.
55–60 dB	996 (23)		0.2 [-0.7; 1.0]
60–65 dB	1200 (28)		0.4 [-0.6; 1.3]
65–70 dB	494 (12)		0.1 [-1.2; 1.3]
>70 dB	171 (4)		1.4 [-1.1; 3.9]
Building density (300 m, at 4–5 years old)	154998 m^2 built/km^2	22	0.8 [0.2; 1.4]
Temperature (Pregnancy)	7.8 °C	20	1.2 [-0.0; 2.5]
Connectivity (300 m, at 4–5 years old)	128 intersections/km^2	16	−0.5 [-1.1; 0.1]
Diastolic Blood Pressure			
Temperature (Day before BP)	11.6 °C	100	−1.1 [-1.6; −0.6]
NO_2 (Pregnancy)	9.1 μg/m^3	82	0.7 [0.3; 1.2]
$PM_{2.5}$ (Year before BP)	3.8 μg/m^3	64	0.9 [0.1; 1.8]
24-h noise (Pregnancy)		24	
<55 dB	1418 (33)		Ref.
55–60 dB	996 (23)		0.4 [-0.4; 1.3]
60–65 dB	1200 (28)		0.8 [-0.0; 1.7]
65–70 dB	494 (12)		0.5 [-0.6; 1.7]
>70 dB	171 (4)		0.2 [-2.1; 2.5]
Temperature (Preg.)	7.8 °C	12	0.6 [-0.6; 1.7]

BP, Blood pressure; CI, Confidence Intervals; DSA, Deletion-Substitution-Addition algorithm; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; SES, Socio-economic status.
* Noise during the night (Ln) and UV at 4–5 years old were selected in 2% of the DSA in association with SBP.
†Change in blood pressure expressed in mmHG for an IQR increment in exposure levels. Estimates are adjusted for co-exposures and the city of inclusion (Bradford, Poitiers, Nancy, Sabadell, Valencia, and Heraklion), maternal age at inclusion (years), maternal pre-pregnancy index (kg/m^2), parity (0, 1, ≥2), native parents of the country of inclusion (both, one, none), maternal education (low, middle, high), child age (months), child sex and child height (cm).

average of all available BP readings.

4.2. Temperature

Ambient temperature is also known to have a short-term effect on blood pressure and cardiovascular events in adults, with a rise in blood pressure with colder temperatures [11]. The few studies that have evaluated the effect of temperature on blood pressure in children, including the present study, reported similar findings, i.e., a negative association between temperature and blood pressure [13,14]. Also, we observed a long-term effect of the average ambient temperature during pregnancy and higher blood pressure in children, a result in line with our previous study performed on 1,300 children (14% overlapped with the present study) at older ages (from 6 to 11 years old) [14]. However, this finding was driven by a single cohort and since temperature was evaluated as an average of the whole pregnancy (and by trimesters), we cannot exclude that this finding reflects more a seasonal effect than a temperature effect.

4.3. Built environment and natural spaces

Characteristics of the built environment in childhood were associated with blood pressure. While higher building density was associated with higher blood pressure, better connectivity in urban transport was associated with lower blood pressure. These associations may reflect how people move around the city and may indicate that more connectivity may promote physical activity. Previous studies have reported that highly walkable environments were associated with lower blood pressure in adults [9]. A protective effect of green spaces observed in the single-exposure was not confirmed after controlling for other related factors such as air pollution or ambient temperature, reflecting potential residual confounding or mediating factors, leading to an overestimation of the effect in the single-exposure models. Similar confounding was recently observed in a study looking at cardiovascular events in adults showing the importance of taking into account correlated exposures in an urban context [39].

4.4. Traffic and noise

In the present study, we did not find evidence of an association between traffic loads, either during pregnancy or childhood, and blood pressure even that a positive association was suggested in the single-exposure associations. Nonetheless, traffic related-noise during pregnancy was identified as predictor of higher blood pressure, and we observed high risk estimates in the ExWAS analysis with both prenatal and postnatal exposure to noise. However, no dose–response trend was observed and the precision of the estimates was limited, most likely due to the small number of subjects exposed to the highest noise level. According to the WHO guidelines, road traffic noise is considered as a risk factor for hypertension in adults, likely due to the physiological stress response, and should not exceed 53 dB; additional longitudinal studies in children are required [8,40].

4.5. Cluster analysis

The cluster analysis revealed 2 subgroups of mother–child pairs that shared similar patterns of unfavourable urban environment and that were associated with a higher blood pressure in children, appearing marginally highest in children living in the inner city than in suburban area despite lower exposure to air pollution, noise and traffic. Together, these two clusters represent 23% of the overall study population. Interestingly, one cluster identified subjects with unfavourable urban environment during pregnancy but not during childhood (among which 90% moved between both periods, in comparison with 49% in the whole study) and for whom no evidence of an increase in blood pressure was observed.

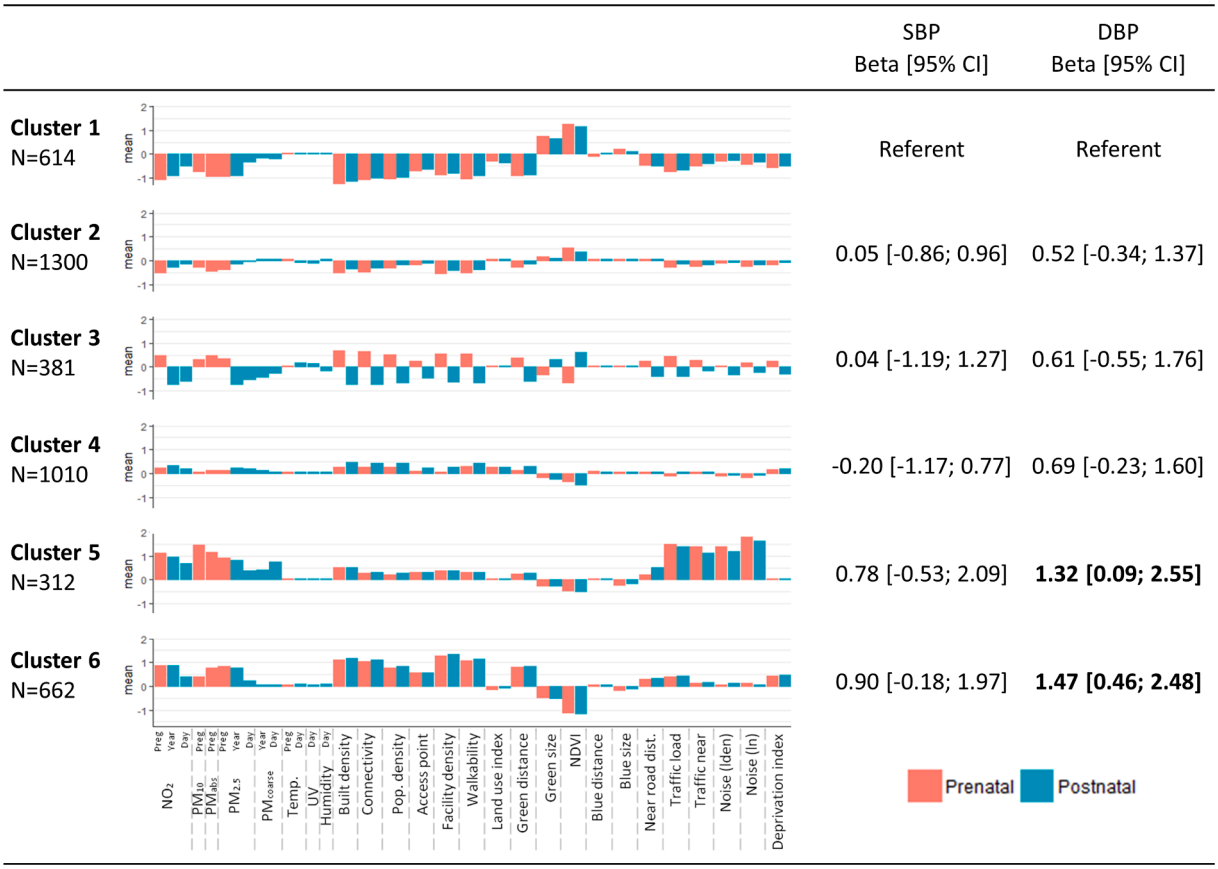

Fig. 2. Description of the urban exposure clusters and their association with blood pressure at 4–5 years old (n = 4,279). The left part of the figure characterizes each cluster for their exposure levels. The height of the bar represents the mean exposure level within the cluster, the mean of the whole study population being 0. Pink bars correspond to prenatal exposures and blue bars to postnatal exposures. The right part of the figure reports the changes [and 95% confidence interval] in blood pressure expressed in mmHG of being in one cluster in comparison with being in cluster 1. The estimates are adjusted for the city of inclusion (Bradford, Poitiers, Nancy, Sabadell, Valencia, and Heraklion), maternal age at inclusion (years), maternal pre-pregnancy index (kg/m^2), parity (0, 1, ≥2), native parents of the country of inclusion (none, one, both), maternal education (low, middle, high), child age (months), child sex and child height (cm). Abbreviations: Lden, Day-evening-night noise level; Ln, night noise level; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of less than 10 μm; PM_{abs}, absorbance of $PM_{2.5}$ filters; PM_{coarse}, particulate matter with an aerodynamic diameter between 2.5 and 10 μm; Preg., average of the whole pregnancy; Temp., Ambient temperature; UV, Ultraviolet radiation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.6. Strengths and limitations

The main strengths of this study is its multi-centre design, including 6 cities from 4 European countries, the wide range of urban factors evaluated at different time points from the prenatal life taking into account the socio-economic area level, and its large sample size compare to existing studies in children. However, we should acknowledge that this study also has several limitations. First, the age range of the participants (4–5 years old) may not be the best time windows for assessing blood pressure which is highly variable at this age and therefore at risk of measurement error. Also, the fact that blood pressure assessment was not standardized among cohorts, due to the use of already collected data, is likely to have introduced between-cohort heterogeneity. Then, the agnostic statistical approach used did not allow to take into account the causal structure between exposures within the urban environment and may have led to an over or under-estimation of effects in case of adjustment for a mediator or a collider. Finally, we acknowledge that some associations (i.e., non-time-varying postnatal exposures) were studied cross-sectionally and could be at risk of reverse causation, and that we cannot exclude a risk of residual confounding due to unmeasured factors.

4.7. Potential biological mechanisms

The biological mechanisms that may be involved in these associations vary according to the time window of exposure. While there is strong evidence for the fetal origins of hypertension, the biological mechanisms remain poorly understood. Some of the suggested mechanisms include epigenetic modifications, placental dysfunction, and impairment in the fetal development of the renal, endothelial or endocrine systems [4]. Several mechanisms have also been proposed in relation to exposure that occurs later in life, especially regarding the effects of chronic and acute exposure to air pollution and noise in adult population [40,41]. These include indirect effects through systemic oxidative stress, inflammation, autonomic imbalance leading to endothelium dysfunction and cardiovascular damage, and, for air pollution, a potential direct effect of particulate matter that may enter into the systemic circulation [40,41].

4.8. Clinical implication

In general, we observed more associations with DBP than with SBP. Although we have no explanation for this result, some of the existing studies in children have reported a similar pattern, i.e., an increase in diastolic but not systolic blood pressure in association with exposure to

air pollution or noise [18,37,38]. However, the clinical relevance of an increase in DBP remains debated, with the literature supporting that SBP is a stronger predictor of cardiovascular morbidity and mortality, and that SBP during childhood tracks better into adulthood than DBP [3,42]. Also, the observed changes in DBP and SBP are relatively small, ranging from around −1 to + 1.5 mmHg for an IQR increase in exposure levels. While such small changes in blood pressure may have little implication at the individual level, they might be clinically relevant at the population level resulting in an increase in the number of subjects classified as hypertensive.

4.9. Implication for policy and research

The urban population of the world has grown rapidly since the 50s and is projected to reach 68% in 2050 [43]. This growth in urbanization will increase the number of people exposed to adverse urban factors and will impact on health and health services over the long term. However the tackling the root causes to prevent such exposures through urban design to promote physical activity and reduce environmental hazards may be more appropriate. There is a growing movement to support urban design that promotes physical and mental well-being. Where there are opportunities to evaluate the health impact of environmental interventions, we would recommend monitoring the impact on blood pressure in early life and over the life course. Further studies taking into the multiple exposures encountered in the urban environment are needed to confirm the reported associations.

5. Conclusion

This study highlights that the urban environment, from conception onward, may affect blood pressure in preschool children. Air pollution, ambient temperature, and noise were among the main determinants of blood pressure in this European multi-city cohort study. Improving urban design and transport planning that reduce adverse environmental exposures has the potential to reduce the risk of cardiovascular diseases in adulthood.

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CRediT authorship contribution statement

Charline Warembourg: Writing - original draft, Formal analysis, Investigation. **Mark Nieuwenhuijsen:** Conceptualization, Writing - review & editing. **Ferran Ballester:** Resources, Writing - review & editing. **Montserrat Castro:** Data curation, Writing - review & editing. **Leda Chatzi:** Resources, Writing - review & editing. **Ana Esplugues:** Resources, Writing - review & editing. **Barbara Heude:** Resources, Writing - review & editing. **Léa Maitre:** Data curation, Writing - review & editing. **Rosemary McEachan:** Conceptualization, Writing - review & editing. **Oliver Robinson:** Methodology, Writing - review & editing. **Rémy Slama:** Conceptualization, Writing - review & editing. **Jordi Sunyer:** Resources, Writing - review & editing. **Jose Urquiza:** Data curation, Writing - review & editing. **John Wright:** Resources, Conceptualization, Writing - review & editing. **Xavier Basagaña:** Methodology, Supervision, Writing - review & editing. **Martine Vrijheid:** Conceptualization, Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no competing financial interests. The funders had no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

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Appendix A. Supplementary material

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