Early life exposure to air pollution, green spaces and built environment, and body mass index growth trajectories during the first 5 years of life: a large longitudinal study

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Abbreviation: BMI = body mass index, IQR = interquartile range, LUR = Land-use-regression model, NO_2 = nitrogen dioxides, PM_{10} = particulate matter (PM) <10 μm, $PM_{2.5}$ = PM <2.5 μm, NDVI = normalized difference vegetation index, SES = socioeconomic status, SIDIAP = Information System for Research in Primary Care.

Highlights

- Large longitudinal study evaluating multiple urban exposures
- Air pollution, green spaces and built environment were associated with small changes in early life BMI trajectories
- Associations were strongest during the first two month of life.
- Important to take into account multiple exposures in urban settings.

Abstract

Urban environments are characterized by multiple exposures that may influence body mass index (BMI) growth in early life. Previous studies are few, with inconsistent results and no evaluation of simultaneous exposures. Thus, this study aimed to assess the associations between exposure to air pollution, green spaces and built environment characteristics, and BMI growth trajectories from 0 to 5 years. This longitudinal study used data from an electronic primary care health record database in Catalonia (Spain), including 79,992 children born between 01/01/2011 and 31/12/2012 in urban areas and followed until 5 years of age. Height and weight were measured frequently during childhood and BMI (kg/m^2) was calculated. Urban exposures were estimated at census tract level and included: air pollution (nitrogen dioxide (NO_2), particulate matter <10μm (PM_{10}) and <2.5μm ($PM_{2.5}$)), green spaces (Normalized Difference Vegetation Index (NDVI) and % green space) and built environment (population density, street connectivity, land use mix, walkability index). Individual BMI trajectories were estimated using linear spline multilevel models with several knot points. In single exposure models, NO_2, PM_{10}, $PM_{2.5}$, and population density were associated with small increases in BMI growth (e.g. β per IQR PM_{10} increase=0.023 kg/m^2, 95%CI: 0.013, 0.033), and NDVI, % of green spaces and land use mix with small reductions in BMI growth (e.g. β per IQR % green spaces increase=-0.015 kg/m^2, 95%CI: -0.026, -0.005). These associations were strongest during the first two months of life. In multiple exposure models, most associations were attenuated, with only those for PM_{10} and land use mix remaining statistically significant. This large longitudinal study suggests that early life exposure to air pollution, green space and built environment characteristics may be associated with small changes in BMI growth trajectories during the first years of life, and that it is important to account for multiple exposures in urban settings

1. Introduction

Childhood obesity is a major public health concern because of the high prevalence levels world-wide ((NCD-RisC), 2017) and because it is associated with serious health consequences in later life including cardiovascular, musculoskeletal and endocrine diseases (Han et al., 2010). Childhood obesity is a multi-factorial disease in which different risk factors play a role at the individual (genetic and non-genetic), family, neighbourhood and community level (Franco et al., 2010). It is increasingly recognized that environmental exposures in urban areas such as air pollution, green spaces, and built environment could have an effect on infant and childhood growth and obesity (An et al., 2018; Galvez et al., 2010; James et al., 2015), and that such effects may start very early in life, during pre and early postnatal periods (Cameron, 2012).

Prenatal exposures to air pollution and lack of green spaces have been associated with fetal growth restriction and lower birth weight (Agay-Shay et al., 2014; Gascon et al., 2016; Li et al., 2017; Markevych et al., 2014; Nieuwenhuijsen et al., 2019; Vrijheid et al., 2016), which are known risk factors for altered growth trajectories during early life (Zheng et al., 2016)). However, little is known about the effect of these prenatal exposures on early postnatal growth. Previous studies on the relationship between prenatal exposure to air pollution and postnatal growth have reported inconsistent results (Fleisch et al., 2019, 2015; Fossati et al., 2020; Kim et al., 2018; Rundle et al., 2019), and, to our knowledge, no previous studies have evaluated the association between prenatal exposures to green spaces and built environment with early postnatal growth. Studies on postnatal exposure in children have studied these exposures mainly at older ages in childhood (6-11 years); these studies have observed inconsistent associations with BMI, growth or obesity for air pollution (An et al., 2018; de Bont et al., 2019; Dong et al., 2015; Fioravanti et al., 2018; Jerrett et al., 2014; McConnell et al., 2015), green spaces (James et al., 2015), and built environment characteristics (Dunton et al., 2009; Feng et al., 2010). Understanding the determinants of postnatal growth in the first years of life is important since early growth is known to have an important influence on the development of childhood and later adulthood obesity (Monteiro and Victora, 2005; Zheng et al., 2018).

With a few recent exceptions (Bloemsma et al., 2019a, 2019b; Klompmaker et al., 2019, 2018; Nieuwenhuijsen et al., 2018), studies on urban exposures and health outcomes have evaluated these exposures individually, thus not accounting for possible confounding or mediating effects of the spatially correlated urban exposures. In this regard, it would be of interest, for example, to account for mutual confounding between air pollution and noise in urban areas because of their common source, traffic (Nieuwenhuijsen 2016), or to consider whether air pollution and noise lie on a causal pathway between green space and growth. No previous studies have assessed the effect of multiple urban exposures on BMI growth trajectories during the first critical years of life.

In this study, we aimed to evaluate associations between early life urban air pollution, green spaces and built environment exposures measured at birth and individual body mass index growth trajectories during the first 5 years of life, using single and multiple exposure approaches.

2. Materials and Methods

2.1. Data Source

This study used prospectively collected data from the Information System for Research in Primary Care (SIDIAP; www.sidiap.com) in Catalonia, Spain (Bolíbar et al., 2012) (Figure S1). SIDIAP contains data from anonymized healthcare records of nearly 6 million people from over 287 primary care centres in Catalonia. It holds longitudinal data from 2006 onwards on anthropometric measurements, disease diagnoses, medication, laboratory tests, demographic and lifestyle information. The SIDIAP population represents around 80% of the Catalan population and is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions (García-Gil et al., 2011).

2.2. Study design and study population

This longitudinal study included 79,992 children born between 1st January 2011 and 31st December 2012, living in urban areas of Catalonia and with at least one height and weight measurement recorded at the same visit during the first year of life. Urban areas were considered areas with more than 10,000 habitants and a population density higher than 150 habitants/km^2 (Figure S2). Children were followed up until they reached 5 years of age, transferred-out of SIDIAP, death, or until the end of the study period (31st December 2016). This study was approved by the Clinical Research Ethic Committee of the IDIAPJGol (code: P16/179).

2.3. Body mass index (BMI) assessment

Height (nearest 0.1 cm) and weight (nearest 100g) were routinely measured following the same protocol by paediatricians and paediatric nurses in primary care centres as part of the "childhood with health" program (Generalitat de Catalunya, 2008). The program recommends measuring height and weight after birth at 30 days, 2 months, 6 months, between 12-15 months, 2 years, and between 3 and 4 years. Height and weight were used to calculate body mass index (BMI) (kg/m^2). BMI z-scores were calculated (WHO Multicentre growth reference study group, 2006). Biologically implausible values of height, weight and BMI (values with z-scores <-5 or >+5) were identified using cut-points proposed by WHO and removed (WHO (World Health Organization), 1995). A conditional growth percentile model was applied to children with more than one measurement to remove implausible values in height and weight trajectories (values with <4 SD or >4 SD the expected conditional height or weight were removed) up to age 5 years (Yang and Hutcheon, 2016).

2.4. Exposure assessment

Exposure assessment was conducted at census tract level. There were 5019 census tracts in Catalonia with a median size of 0.12 km^2 and a median population density of 12,857 (5^{th} percentile = 13 persons/km^2; 95^{th} percentile = 71338 persons/km^2). The exposure level of each child was set to the census track location of their baseline residence, which was defined as the first BMI measurement (for 96% of the dataset this was at birth). Data sources and time periods of the different exposure assessments are specified in table S1.

2.4.1. Ambient air pollution

We estimated 2009 annual census residential levels of nitrogen dioxides (NO_2), nitrogen oxides (NO_x), particulate matter <10 μm (PM_{10}), between <10 μm and <2.5 μm (PM_{coarse}), <2.5 μm ($PM_{2.5}$) and $PM_{2.5}$ light absorption ($PM_{2.5abs}$) using a land use regression (LUR) model developed within the ESCAPE framework for Catalonia; a detailed description can be found elsewhere (Beelen et al., 2013; Eeftens et al., 2012). The LUR model predicted 62-76% of the variation in pollutant levels in our study area during 2009. To estimate at census level, an artificial grid points data set with *n* random points was created within each census tract based on its area, thus increasing the density of points in smaller areas and reducing the number of points in larger areas. We ensured that at least 5 observations predicted within each census areas. Air pollution was then averaged by census area (Nieuwenhuijsen et al., 2018).

2.4.2. Green space

Two definitions of green spaces were estimated for each census tract. First, the Normalized Difference Vegetation Index (NDVI) was used to assess average greenness of each census tract. The NDVI was derived from the Landsat 8 at a spatial resolution of 30 m. NDVI is an indicator of greenness based on the difference between visible red and near-infrared surface reflectance. NDVI values range from -1 to +1, with higher values indicating more greenness (Weier J and Herring D, 2000). Negative values correspond to water bodies and were set to zero. We obtained cloud-free images within the greenest season (April to July) during 2010–2014 and then we averaged them. Second, the percentage of green space was calculated as the area covered by of green space within a census tract derived from the land cover map of Catalonia from 2009 (CREAF, 2009). On both exposures, we added a 300 meter buffer to the census tract estimates to account for surrounding greenness.

2.4.3. Built environment characteristics

Several built environment characteristics were estimated using different data sources for the years nearest to our study period (table S1). Population density and household density were calculated as the number of inhabitants and number of households, respectively, divided by the census area (km^2). Street connectivity was defined as the number of intersections that are not dead-ends, divided by the census track area. Land use mix (Shannon's Evenness Index) was calculated to provide the proportional abundance of each type of land use in the census track plus a 300 meter buffer, using the

land cover map of Catalonia. Finally, we developed an indicator of walkability, adapted from previous walkability indexes (Duncan et al., 2011; Frank et al., 2006), calculated as the mean of the deciles of population density, street connectivity, facility richness index, and land use mix in each census, giving a walkability score ranging from 0 to 1.

2.5. Covariates

From SIDIAP, we obtained individual level covariates, including sex, age and child nationality. Information on socioeconomic status (SES) was available through the deprivation MEDEA index at census track level (Domínguez-Berjón et al., 2008). The deprivation index is based on 5 indicators related to work (unemployment, manual and eventual workers) and education (insufficient education overall and in young people) obtained from the Spanish national census of 2001. This indicator was stratified in quintiles based on the whole region of Catalonia and not on our specific study population. The 1^{st} and 5^{th} quintiles were the least and most deprived areas, respectively. This indicator was only available for urban areas. Nationality was grouped in 5 categories: Spanish, African, North/Central/South American (98.4% were from Central and South America), Asian and European. Further, we identified all "movers", i.e. children that changed residency at least once during follow-up. Additionally, for 68% of the children in SIDIAP, mother and child were linked through the number of affiliation to the social security; a detailed description can be found elsewhere (Duarte-Salles et al., 2018). With the mother-child linkage we were able to get information on maternal socioeconomic and lifestyle characteristics including smoking during pregnancy (yes/no) and pre-pregnancy maternal BMI (kg/m^2).

For around 52% of the study population we were able to calculate average census noise levels. These were calculated as the average sound pressure level over all days, evenings, and nights in the year 2012 (L_{den}) and obtained from the Strategic Noise Map of Catalonia (Generalitat de Catalunya, 2012). The map was developed with a set of standardised noise measurements, according to the Environmental Noise Directive 2002/49/EC (European Commission, 2002). To estimate at census level, we overlaid the street-level noise maps with the census tracts and we averaged exposure after a noise length weight procedure (Nieuwenhuijsen et al., 2018). Noise exposure values were available for 70% of the areas with more than 100,000 persons and a population density more than 3,000 people/km^2.

2.6. Statistical analyses

2.6.1. Building the statistical model

We fitted a linear spline multilevel model that estimated childhood individual BMI growth trajectories from birth until the age of 5. We included all children with at least one BMI measurement under a missing at random assumption. We modelled BMI trajectories at two levels: a specific occasion-level (level 1) that captures the measurement error in the BMI values, and an individual-level (level 2) that captures each individual's deviation from the average trajectory (Howe et al., 2016).

The non-linear relationship between BMI and age was modelled using a linear spline with several knot points. To visualize the possible knot points, we first fitted the best fitting-curve with a fractional polynomial and we identified the possible number and timing of the knot points selection. Then, we evaluated several models with different knot points location (from 2 to 5 knot points) around different time periods where a larger number of BMI measurements were available in our dataset (this was at 2 months, 6 months, 12 months, 24 months and between 36 and 48 months). The best-fitting linear spline model was selected by comparing the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of different models and the percentage of predicted values within 5% of the observed values (Howe et al., 2016). The linear spline multilevel model we selected had knot points at 2, 6 and 24 months (Figure S3). Furthermore, to account for differences in BMI trajectories between boys and girls, sex was included as an interaction term with each spline period. Since the measurement error of height and weight vary over time, we also modelled the complex level 1 variation. We did this by allowing the within-subject variation to change over time by adding three constant terms at level 1 for time periods 0-2 months, 2-6 months and 6-60 months (n.b., we merged the last two spline periods to aid convergence). All analyses were conducted using the *runMLwiN* command in R (version 3.5.1.) that calls the MLwiN program (Rabash et al., 2009; Zhang et al., 2016).

2.6.2. Single exposure models

The linear spline multilevel model was fitted to evaluate the single associations between each urban exposure on BMI growth. We added each urban exposure as a fixed effect and assumed the urban exposure had the same effect on BMI trajectories across all spline periods. The main model for each exposure was adjusted for sex (as an interaction term with each spline period), deprivation index and nationality. Levels of urban exposures were assigned at baseline and were kept constant for all spline models. In all the models we treated the exposure levels as continuous variables (interquartile [IQR] increase).

2.6.3. Multiple exposure models

We developed multiple exposure models in order to evaluate possible confounding or mediating effects of the spatially correlated urban exposures. We identified the potential pathways linking each urban exposure to BMI growth based on a DAG, and selected confounders for each urban exposure individually (Supplement Figure S4). Based on this DAG, we considered green spaces and built environment characteristics to be mutual confounders as they are part of the urban design. Further, green spaces and built environment characteristics can partly determine the levels of air pollution in a city and air pollution may thus be on the causal pathway from these exposures to BMI growth. Therefore, we added air pollution in the models for green space and built environment as possible mediator (to date, it is not possible to apply a causal mediation framework in the *runMLwiN* package), and evaluated if the effect estimates for green spaces and population density changed when we included air pollution in the model (Preacher and

Kelley, 2011)Finally, we adjusted the association between air pollution and BMI growth for green spaces and built environment as they are considered confounders (Supplement Figure S4).

The indicators within each group of exposures (air pollution, green spaces and built environment) are highly correlated. Thus, we selected only one indicator for each exposure group for the multiple exposure models. For this, we used the indicator which was most strongly associated with BMI in the single-exposure models. We estimated variance inflation factors (VIFs) to estimate the multicollinearity between the exposures.

2.6.4. Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of our results: a) we added an interaction term between the exposure and each spline term (exposure-spline interaction model). This exposure-spline interaction model allows the effect of the exposure on BMI to differ between each spline period, including the baseline at birth, and estimates the effect of exposure on BMI growth per year for each spline period. b) we evaluated potential effect modification by socio-economic status by stratifying our analysis by quintiles of the deprivation index; c) we stratified the analyses by movers (children that changed residency at least once during follow-up) and non-movers; d) we evaluated whether maternal smoking during pregnancy and pre-pregnancy maternal BMI were potential confounders using the reduced mother-child linked dataset; e) we evaluated whether noise exposure was a confounder in the association between air pollution and BMI growth using the reduced dataset with available noise estimates. f) We excluded children who were born preterm (< 37 gestational week) and children born <2.500g regardless gestational age, as this children may affect BMI trajectories significantly.

3. Results

Study population

In our study population (N=79,992), 49% of children were girls, 23% lived in the most deprived areas and 83% had Spanish nationality. Children were followed up for an average of 4.7 years and had a median of 11 BMI measurements during the follow-up (Table 1). During the 5-year follow-up period 18% changed their census residency at least once.

Urban exposure distribution

The percentage of the children living in census tracts with median annual levels of NO_2, PM_{10} and $PM_{2.5}$ above the WHO guidelines (<40, <20 and <10 $\mu g/m^3$, respectively), was more than 75% for PM_{10} and $PM_{2.5}$ and 50% for NO_2 (Table 1). Children lived in census tracts with a median of 11.9% of green spaces and 19,299 people/km² of population density. Figure S5 shows the spearman correlation between the different urban exposures in the full dataset. The air pollutants were negatively correlated with

green spaces exposures and walkability (r_s =-0.3 to -0.7), and positively correlated with the other built environment characteristics (r_s = +0.2 to +0.6). Green spaces were positively correlated with walkability (r_s = 0.7) and negatively correlated with the other built environment characteristics (r_s = -0.3 to -0.6). Highly correlated urban exposures (r_s > 0.9) were excluded from the analyses, including NO_x and PM_{abs} (correlated with NO_2), PM_{coarse} (correlated with PM_{10}), and household density (correlated with population density).

Single exposure models

In single exposure models we observed that NO_2, PM_{10}, $PM_{2.5}$ and population density were associated with a small increase in BMI growth from birth until the age of 5 (Figure 1 and Table S2). The average increase in BMI over these 5 years for each 21.3 $\mu g/m^3$ (IQR) increase in NO_2 exposure was 0.018 kg/m^2 [95%CI: 0.006, 0.030]. Effect estimates were of similar magnitude for the other air pollutants (PM_{10}: β = 0.023, [95%CI: 0.013, 0.033]; $PM_{2.5}$: β=0.007, [95%CI: 0.000, 0.013]) and population density (β=0.019, [95%CI: 0.007, 0.030]). In addition, we observed that NDVI, % of green spaces and land use mix were associated with a small reduction in BMI from birth until the age of 5 (NDVI: β = -0.011, [95%CI: -0.021, -0.002]; % green spaces: β = -0.015, [95%CI: -0.026, -0.005], land use mix: β = -0.027, [95%CI: -0.042, -0.012]). There was no association between street connectivity or walkability score and BMI growth. Crude models (not adjusting for deprivation index and nationality), gave very similar results for all exposures (Table S2).

In sensitivity analyses, the exposure-spline interaction model, showed that associations were strongest in the 0-2 month period (spline 1) (Table 2). In the other periods, i.e. 2-6 months (spline 2), 6-24 months (spline 3) and 24-60 months (spline 4), the associations between the exposure and BMI growth were weak and did not reach statistical significance. Further sensitivity analyses showed that effect estimates were largely similar across quintiles of the deprivation index for most exposures; NDVI, % green spaces and land use mix showed somewhat stronger association with reduced BMI growth in the first and fifth quintiles than in the other quintiles (Figure S6). When restricting the study population to movers the associations between the urban exposures and BMI growth remained similar as in the entire population (Table S3). Effect estimates for the associations between the urban exposures and BMI growth did not change substantially after adding maternal smoking during pregnancy and pre-pregnancy BMI to the model in the reduced dataset with linked maternal data (Table S4). In the reduced population with noise data, the effect estimates of air pollution were not significant and they did not change after adjustment for noise (Table S5). Excluding children born premature or children born <2.500g regardless gestational age did not changed the effect estimates (Table S6).

Multiple exposure models

Urban exposures that were associated with BMI growth single exposure models were evaluated in the multiple exposures models (Figure 2 and Table S7). The effect

estimates of PM_{10} and land use mix remained similar after adjusting by other urban exposures (PM_{10} (β) = 0.020 [95% CI: 0.008, 0.033]; land use mix (β) = -0.023, [95%CI: -0.043, -0.003]). Effect estimates for NO_2, $PM_{2.5}$, % green spaces, NDVI and population density were attenuated and no longer statistically significant after adjusting for other urban exposures (Figure 2 and Table S6). When we added air pollution as mediator to models for green spaces and built environment effect estimates attenuated. The VIF values ranged from 1.3 through 2.3 indicating no multicollinearity among the different urban exposures.

4. Discussion

In this large longitudinal study, we were able to assess for the first time the association between multiple early life urban exposures and spline-based BMI growth trajectories during the first 5 years of life. In single exposure models, we found that NO_2, PM_{10}, $PM_{2.5}$, and population density were associated with increased BMI growth, whereas NDVI, % of green spaces and land use mix were associated with reduced BMI growth. The associations between the exposures and BMI growth appeared strongest during the first two months of life. In multiple exposure models, most associations were close to the null and no longer statistically significant after adjustment for potential confounding by other exposures or when air pollution was added as potential mediator; only those for PM_{10} and land use mix remained statistically significant. Overall effect estimates were small.

Early life includes prenatal and early postnatal periods, representing windows of particular vulnerability to the influence of environmental exposures, because of the rapidly changing growth rates during these years and because environmental exposures may permanently change the structure, physiology and metabolism of the child's body (Dietz, 1994; Gluckman and Hanson, 2004). We assigned exposures around the time of birth in order to represent both prenatal and early postnatal life exposures as it was not possible to separate these periods in our data. In any case, urban exposures for those who do not move would not be expected to change substantially during our study period, thus making it impossible to distinguish between periods. Our findings therefore suggest that exposure to air pollution, green spaces and built environment during these two periods may alter childhood BMI growth trajectories before the age of 5, especially during the first two month of life. We suggest that the stronger associations observed in the earliest part of the growth trajectories may be explained by an effect of exposure during pregnancy. Prenatal exposure to air pollution has quite consistently been associated with fetal growth restriction and lower birth weight (Li et al., 2017; Vrijheid et al., 2016), which are known risk factors for faster growth trajectories during the first months of life (Claris et al., 2010; Zheng et al., 2016). Further, several studies have documented an association between green space exposure during pregnancy, and faster fetal growth and higher birth weight (Agay-Shay et al., 2014; Markevych et al., 2014; Nieuwenhuijsen et al., 2019). Our findings suggests that effects on fetal growth and birth weight may continue after birth and resulting in faster BMI growth for air pollution and maybe population density, and slower BMI growth for green spaces and

land use mix. We note that for air pollutants, the stronger associations observed in the first 2 months after birth appear to be followed by reversal of the association between month 2 and 6, where we observe slower BMI growth with increased air pollution exposure. Further, in the first 2 months, we also observed that BMI growth increased with PM_{10} exposure but decreased slightly, and non-statistically significantly with $PM_{2.5}$ exposure despite the high correlation between these two pollutants ($r_s = 0.74$). We don't have a clear explanation for this result, but speculate that this could be related with the narrow range of $PM_{2.5}$ (IQR of 1.5 $\mu g/m^3$) obscuring any positive association. The effects of different air pollutants on very early postnatal growth trajectories require replication in future studies.

Regarding air pollution, the few studies that assessed the role of prenatal air pollution exposure to postnatal BMI growth have inconsistent results (Fleisch et al., 2019, 2015; Fossati et al., 2020; Kim et al., 2018; Rundle et al., 2019). A prospective cohort in Massachusetts (US) evaluated BMI at birth (N=1838) and at 6 months (N=1030), they observed that prenatal exposure to air pollution was associated with reduced foetal growth and rapid weight gain (Fleisch et al., 2015). A cohort study in Boston (US) followed 1649 children from 10 weeks of gestation until 7.7 years of age and did not find an association between prenatal exposure to traffic pollution ($PM_{2.5}$) and BMI growth trajectories (Fleisch et al., 2019). A small (N=535) New York cohort study reported no association between prenatal exposure to airborne polycyclic aromatic hydrocarbons and BMI z-score trajectories (Rundle et al., 2019). Finally, a study in Southern California (N=2.318) evaluated both prenatal and postnatal exposure on postnatal BMI growth. This study reported increased BMI growth between 6.5 and 9.5 years of age with increased traffic related air pollution (NO_x) during the first year of life, but did not find an association for prenatal exposure (Kim et al., 2018). However, they found prenatal and postnatal exposures to be highly correlated and were unable to conclude which exposure time period contributed more to BMI growth. Finally, a Spanish birth cohort of 1724 mother-child pairs found that higher exposure of air pollution in the first trimester of pregnancy was associated with increased risk of being in a trajectory with accelerated BMI gain between birth and four years (Fossati et al., 2020). Overall, the effect estimates in these studies were small and of similar magnitude to those observed in our study (in the order of a few decimals of BMI increase per year per IQR increase in air pollution). Studies on air pollution exposures during mid-childhood (4-11 years) have reported an increased BMI or risk of childhood obesity with increased levels of exposure (de Bont et al., 2019; Dong et al., 2015; Jerrett et al., 2014; McConnell et al., 2015); null associations (Fioravanti et al., 2018; Frondelius et al., 2018) and lower obesity risks have also been reported (An et al., 2018). Our study suggests that associations between NO_2 and $PM_{2.5}$, but not PM_{10}, and BMI growth may be partly explained by green spaces and built environment characteristics. This may be explained by the fact that NO_2 and $PM_{2.5}$ are more related to traffic in urban areas than PM_{10} (HEI (Health Effects Institute), 2010; Pérez et al., 2010), and thus could be more influenced by adjusting for other urban exposures related to traffic. At the same time, we should note that the high correlations between air pollution and built environment

characteristics (correlation coefficients up to 0.6 in our data) would always make it hard to separate air pollution effects from those of other urban exposures.

The biological mechanisms underlying the effect of air pollution and BMI growth are starting to emerge. Some animal studies have observed that pre-natal exposure to air pollution affects fetal growth and reduced birth weight in mice (Blum et al., 2017; Weldy et al., 2014). Air pollution is suggested to alter fetal growth through oxidative stress, inflammation, alter placental growth and foster endocrine disruption, among others (Kannan et al., 2006). One mice study found that in *utero* exposure to diesel exhaust reduced low birth weight and increased body weight in adult mice (Weldy et al., 2014). In addition, prenatal exposure to air pollution may also affect neuroinflammation on the brain stimulating appetite or anxiety inducing over-eating in adult mice (Bolton et al., 2012). Post-natal exposure of air pollution can affect basal metabolism known to increase obesity by inducing insulin resistance, visceral inflammation and adiposity, and hormone disruption in mice (Sun et al., 2009; Xu et al., 2010). The basal metabolism can be affected also through an inflammatory effect of air pollution on other tissues, including the cardio-respiratory system (Haberzettl et al., 2016; Wei et al., 2016).

To our knowledge, ours is the first study to assess the association between early life exposure to urban green spaces and BMI growth during early childhood years; our results indicate that green space exposure may be associated with reduced BMI growth up to 5 years of age, and particularly in the first two months of life, although this association was attenuated when built environment characteristics (a confounder for this association) or air pollution (a potential mediator) were added to the models. Previous studies in older children (evaluating childhood exposure) were largely of cross-sectional design and showed mixed results (James et al., 2015). The attenuation of our green space association after adjustment for population density shows the importance of including wider urban environment characteristics as potential confounders in green space studies. The underlying mechanisms for the inverse association between green spaces and early BMI growth could be explained mainly through two different pathways. First, green spaces are a valuable source for physical activity for the mother and the child and therefore have the potential beneficial effect on the development of both the fetus and the young child (Dadvand et al., 2019; James et al., 2015). Second, the potential association between green spaces and BMI growth could be explained through a reduction of air pollution levels in greener areas during pregnancy and first year of life (Markevych et al., 2017). Supporting this, in our study we observed an attenuation of the effect of green spaces on BMI growth after adjusting for air pollution, indicating possible mediation. Each of these pathways requires further elucidation (James et al., 2015; Lee and Maheswaran, 2011; Markevych et al., 2017)

Our study is one of the first studies to evaluate the influence of early life exposure of the urban built environment on post-natal BMI growth; our results indicate that population density maybe associated with increased BMI growth, whereas land use mix is associated with decreased BMI growth. However, only land use mix remained similar after adjusting for green spaces. To our knowledge, prenatal exposure to built

environment characteristics has not been studied in relation to postnatal growth. Only one previous study evaluated the associations between many urban exposures during pregnancy and birth weight (Nieuwenhuijsen et al., 2019). They did not report consistent associations between built environment characteristics (including building density, facility density, street connectivity and land use mix) and birth weight after adjusting for other urban exposures (Nieuwenhuijsen et al., 2019). Studies on postnatal exposure to the built environment and obesity during mid-childhood, adolescence or adulthood, have associated areas with lower population density with higher levels of childhood obesity, whereas greater land use mix and walkability of neighbourhoods have been associated with lower levels of childhood obesity (Dunton et al., 2009; Feng et al., 2010). The effect of less populated areas on childhood obesity may be explained through reduced levels of physical activity in the US (Feng et al., 2010). Conversely, in our Spanish setting, increased population density was associated with increased BMI growth. In our setting, more populated areas represent higher traffic intensity which may be associated with perceived lack of safety among children and parents, and would reduce active commuting and increase childhood obesity (Huertas-Delgado et al., 2017). Another explanation is that more populated areas have higher levels of air pollution which could be associated with BMI growth. Supporting this, we observed an attenuation of the effect of built environment characteristics on BMI growth after adding air pollution to the models, indicating possible mediation. Our finding of reduced BMI growth with increasing land use mix is in line with previous studies (Feng et al., 2010). There is no clear consensus how land use mix affects body mass index (Nieuwenhuijsen, 2016). The main hypothesis is that increased land use mix decreases distances between home, work and amenities, thereby it reduces trips distances, increasing active modes of transport and levels of physical activity, thus affecting BMI (Feng et al., 2010). Land use mix is one of the built environment characteristics contributing to walkability; our results suggest that land use mix indeed has a beneficial effect on BMI growth and further detailed studies are needed to examine which environmental factors or individual behaviours might explain this.

Major strengths of this study are its longitudinal design, its large sample size covering urban areas in the entire Catalan region (nearly 80.000 children), its assessment of multiple urban exposures, and its use of repeated BMI measurements over time. We developed BMI growth trajectories during early life based on multiple splines to characterise detailed growth patterns. Linear spline multilevel model are a simplification of growth trajectories and they assume linear growth. BMI has clearly a nonlinear growth between 0-5 years, but we minimized non-linearity by adding several knot points (at 2, 6 and 24 months). Further, linear models are more interpretable than non-linear models and the results can be compared across populations (Howe et al., 2016; Tu et al., 2013). Our study applied single and multiple exposure models to look at each factor individually, accounting for other urban exposures as confounders or mediators. There are few previous studies that have included this type of assessment. Although new approaches have been proposed to study multiple urban exposures, including multipollutant models (Dominici et al., 2010), the exposome framework

(Agier et al., 2016) and joint effect models (Tanner et al., 2020), there is no clear consensus on the best methods to use. Future studies should consider these different approaches depending on their research aims.

Our study also faced some limitations. Our exposure assessment was aggregated at census track level, reducing individual variability and accuracy. This may have introduced misclassification, especially for air pollution exposure as it tends to be more local and with higher variability. However, we expect that this misclassification to be non-differential as the exposures were estimated independently from health outcomes and potential confounders, systematic error would be unlikely and would bias effect estimates towards the null (Nieuwenhuijsen, 2015) For green spaces and built environment we expect to introduce more misclassification in larger census areas that are less populated. Further, our air pollution levels are estimated in 2009, before our study period (2011-2012), which could have led to misclassification. However, studies have found that the spatial variation of air pollution levels using the land use regression model remains stable over periods of 10 years (Eeftens et al., 2011). We cannot entirely rule out residual confounding as an explanation for our findings. First, we did not have information on individual behaviours related to obesity, particularly diet and physical activity. Also, although we adjusted for census deprivation index and child's nationality, residual confounding by individual socioeconomic status cannot be ruled out. However, levels of our urban exposures varied little by quintiles of the deprivation index (data not shown) and our models adjusting and not adjusting for deprivation gave very similar results, indicating that deprivation had little confounding effect in our models. Furthermore, in our sensitivity analysis maternal smoking and BMI during pregnancy, two variables related to socioeconomic status, did not confound the observed associations. Lastly, we were only able to test the confounding effect of noise in a reduced dataset in which only PM_{10} showed an association with BMI growth.

Finally, we highlight that although the small changes in BMI growth observed in this study may not be clinically important on an individual level, they may have an impact at the population level. We calculated that children exposed to the 90^{th} percentile of NO_2 and NDVI had a predicted BMI at 5 years of 15.98 kg/m^2 and 15.86 kg/m^2, respectively, whereas children exposed to the 10^{th} percentile the predicted BMI was 15.86 kg/m^2 and 15.93 kg/m^2, respectively. Nowadays, 80% of the children in SIDIAP live in urban areas and have widespread exposure to the urban factors we included in our study; even small changes in BMI at these early ages may be important at a population level over the longer term.

To conclude, this large longitudinal study suggests that early life urban exposure to increased levels of air pollution and population density may be associated with a small increase in BMI in very young children, whereas green spaces and land used may be associated with a small decrease BMI. Stronger associations were observed during the first two month of life. Future studies should take account of multiple urban exposures in urban settings.

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CRediT authorship contribution statement

Jeroen de Bont: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Rachael Hughes:** Methodology, Validation, Formal analysis, Writing - review & editing. **Kate Tilling:** Methodology, Formal analysis, Writing - review & editing. **Yesika Díaz:** Data Curation, Writing - review & editing. **Montserrat de Castro:** Investigation, Resources, Writing - review & editing. **Marta Cirach:** Investigation, Resources, Writing - review & editing. **Serena Fossati:** Methodology, Writing - review & editing. **Mark Nieuwenhuijsen:** Methodology, Writing - review & editing. **Talita Duarte-Salles:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Resources, Writing - review & editing. **Martine Vrijheid:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Resources, Writing - review & editing.

Declaration of competing interest

All authors declare no conflict of interest

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Table 1: Child baseline characteristics and urban exposure distribution of the study population (N=79,992).

	Study population N=79,992
Baseline characteristics	
Age at baseline, median years (p25; p75)	0.0 (0.0; 0.0)
Girls, N %	38,940 (48.7%)
Deprivation index (quintiles), N %	
First (Least deprived)	13,539 (16.9%)
Second	15,314 (19.1%)
Third	16,012 (20.0%)
Fourth	16,778 (21.0%)
Fifth (Most deprived)	18,349 (22.9%)
Nationality, N %	
Spain	66,532 (83.2%)
Africa	7436 (9.3%)
America	1370 (1.7%)
Asia	2642 (3.3%)
Europe	2012 (2.5%)
Years of follow-up, means (SD)	4.7 (0.6)
Number of BMI measurements, median (p25; p75)	11 (9; 13)
Moved during follow-up, N %	14,937 (18.7%)
Mothers with information on smoking during pregnancy and maternal pre-pregnancy BMI, N %	30,487 (38.1%)
Smoking during pregnancy, N %	9676 (31.7%)
Maternal pre-pregnancy BMI, mean kg/m^2 (SD)	24.9 (4.8)
Noise data available, N %	41,676 (52.1%)
Noise levels (dB(A)) , median (p25; p75)	63.3 (60.7;66.1)
Gestational age, N %	
Born at term	67,857 (84.8%)
Born preterm	5554 (6.9%)
Missing	1027 (8.2%)
Birth weight, N %	
Born ≥2500 g	71,400 (89.3%)
Born <2500 g	5657 (7.1%)
Missing	1027 (3.7%)
Urban exposures distribution	
Air pollution:	
NO_2 (μg/m^3), median (p25; p75)	43.4 (30.8; 52.1)
PM_{10} (μg/m^3), median (p25; p75)	35.0 (31.9; 38.1)
$PM_{2.5}$ (μg/m^3), median (p25; p75)	14.9 (14.1; 15.5)
Green spaces:	
NDVI , median (IQR)	0.2 (0.2;0.3)
% green spaces , median (p25; p75)	11.9 (0.8; 34.0)
Built environment:	
Population density (people/km^2), median (p25; p75)	19,299.8 (6515; 40533)
Street connectivity (intersections/km^2), median (p25; p75)	182.5 (107.3; 275,4)
Land use mix, median (p25; p75)	0.3 (0.1; 0.5)
Walkability index, median (p25; p75)	0.6 (0.5, 0.7)

p25 = 25th percentile, p75 = 75th percentile, NO_2 = nitrogen dioxides, PM_{10} = particulate matter (PM) <10 μm, $PM_{2.5}$ = PM <2.5 μm, Lden = annual average of day, evening and night noise levels, NDVI = normalized difference vegetation index. Values are mean (SD) for continuous normal distributed variables, median (interquartile range) for continuous non-normal distributed variables, and percentage for categorical variables

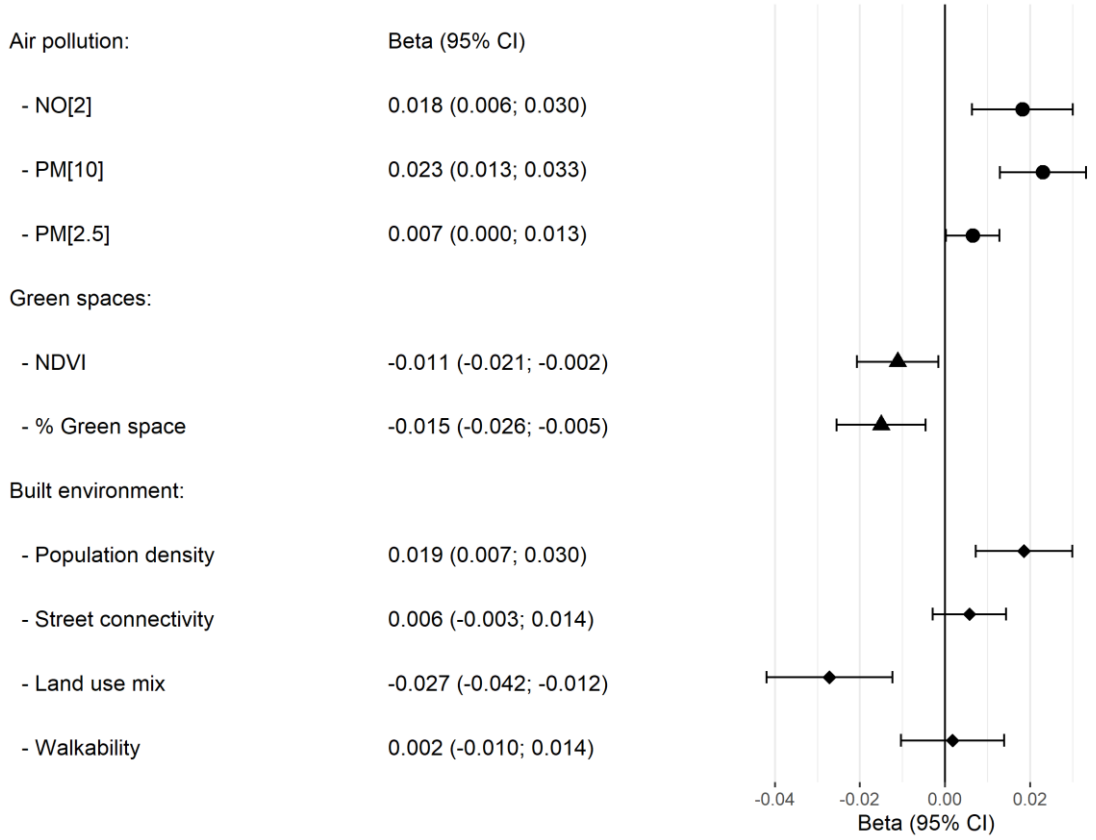
Table 2: Associations between urban air pollution, green spaces and built environment, and BMI growth for each period.

Urban exposures	BMI growth (N=79,992)			
	0-2 months (spline 1) β[a] (95% CI)	**2-6 months (Spline 2) β[a] (95% CI)**	**6-24 months (Spline 3) β[a] (95% CI)**	**24-60 months (Spline 4) β[a] (95% CI)**
Air pollution				
NO_2 (per 21.3 μg/m^3)	0.109 (0.021; 0.198)	-0.059 (-0.099; -0.020)	-0.002 (-0.011; 0.008)	0.022 (0.016; 0.029)
PM_{10} (per 6.3 μg/m^3)	0.096 (0.020; 0.172)	-0.033 (-0.066; 0.001)	-0.011 (-0.019; -0.003)	0.016 (0.010; 0.022)
$PM_{2.5}$ (per 1.5 μg/m^3)	-0.042 (-0.089; 0.004)	-0.020 (-0.041; 0.001)	0.004 (-0.001; 0.009)	0.004 (0.000; 0.008)
Green spaces				
NDVI (per 0.1 units)	-0.191 (-0.263; -0.119)	0.002 (-0.029; 0.034)	0.012 (0.004; 0.019)	-0.012 (-0.017; -0.006)
% Green (per 33.2 % units)	-0.177 (-0.255; -0.099)	0.020 (-0.015; 0.055)	0.001 (-0.007; 0.009)	-0.007 (-0.013; -0.001)
Built environment				
Population density (per 34018 people/km^2)	0.341 (0.257; 0.424)	-0.027 (-0.064; 0.010)	-0.007 (-0.016; 0.002)	0.015 (0.008; 0.021)
Street connectivity (per 168 intersection/km^2)	0.105 (0.040; 0.169)	-0.005 (-0.034; 0.024)	-0.002 (-0.009; 0.004)	0.005 (0.000; 0.010)
Land use mix (per 0.4 units)	-0.236 (-0.347; -0.125)	0.001 (-0.049; 0.05)	0.003 (-0.009; 0.015)	-0.011 (-0.019; -0.002)
Walkability index (per 0.2 units)	-0.052 (-0.142; 0.038)	-0.005 (-0.046; 0.035)	0.001 (-0.008; 0.011)	-0.005 (-0.012; 0.002)

Note: NO_2 = nitrogen dioxides, PM_{10} = particulate matter (PM) <10 μm, $PM_{2.5}$ = PM <2.5 μm, NDVI = normalized difference vegetation index. Models were adjusted by sex, deprivation index and nationality.

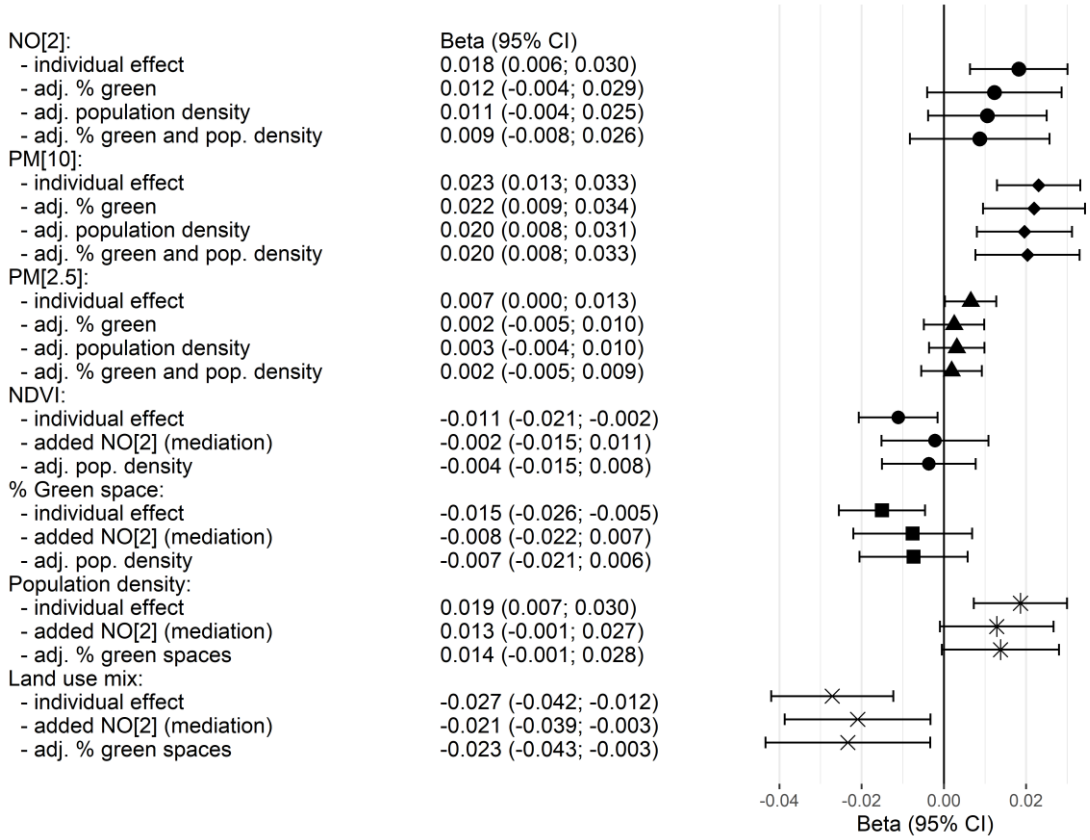
[a] beta values represent the BMI (kg/m^2) growth rate change per year for each IQR increase in exposure.

Figure 1: Associations between urban air pollution, green spaces and built environment, and BMI growth during the first 5 years of life (beta values represents the average difference in BMI (kg/m^2) for each IQR increase in exposure). This figure corresponds to supplement table S2.



Models adjusted by sex, deprivation index and nationality. Associations are shown for an interquartile range increase in exposure.

Figure 2: Associations between urban air pollution, green spaces, and built environment, and BMI growth in multiple exposure models (beta values represents the average difference in BMI (kg/m^2) for each IQR increase in exposure). This figure corresponds to supplement table S6.



All models were adjusted for age, sex, deprivation index and nationality. Associations are shown for an interquartile range increase in exposure.