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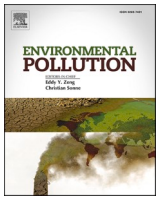

Urban environment during pregnancy and lung function, wheezing, and asthma in school-age children. The generation R study☆

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ABSTRACT

The urban environment during pregnancy may influence child's respiratory health, but scarce evidence exists on systematic evaluation of multiple urban exposures (e.g., air pollution, natural spaces, noise, built environment) on children's lung function, wheezing, and asthma development.

We aimed to examine the association of the urban environment during pregnancy with lung function, preschool wheezing, and school-age asthma.

We included 5624 mother-child pairs participating in a population-based prospective birth cohort. We estimated 30 urban environmental exposures including air pollution, road traffic noise, traffic, green spaces, blue spaces, and built environment during pregnancy. At 10 years of age, lung function was measured by spirometry. Information on preschool wheezing and physician-diagnosed school-age asthma was obtained from multiple questionnaires. We described single-exposure associations with respiratory outcomes using an exposome-wide association study. We also identified patterns of urban exposures with hierarchical clustering on principal components analysis and examined their associations with respiratory outcomes using multivariate regression models.

Single-exposure analyses showed associations of higher particulate matter (PM) with lower mid-expiratory flow ($FEF_{25-75\%}$) (e.g., for PM < 2.5 μm of diameter [$PM_{2.5}$] z-score = −0.06 [-0.09, −0.03]) and higher forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC) (e.g., for $PM_{2.5}$ FEV_1 0.05 [0.02, 0.08]) after correction for multiple-hypothesis testing. Cluster analysis described three patterns of urban exposures during pregnancy and showed that the cluster characterised by higher levels of air pollution, noise, walkability, street connectivity, and lower levels of natural spaces were associated with lower $FEF_{25-75\%}$ (−0.08 [-0.17, 0.00]), and higher odds of preschool wheezing (1.21 [1.03, 1.43]).

This study shows that the characteristics of the urban environment during pregnancy are of relevance to the offspring's respiratory health during childhood.

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1. Introduction

Lung function and asthma development during childhood are key determinants for respiratory health into adult life (Melén and Guerra, 2017). Early life, particularly the pregnancy period, is a critical stage of development that is especially vulnerable to environmental exposures. Exposures occurring in that period may have long-term health implications (Barker, 2007; Miller and Marty, 2010). Many early life environmental exposures are associated with the development of lower lung function and risk of asthma in childhood (Garcia et al., 2021; Khreis et al., 2017; Gehring et al., 2020; Fuertes et al., 2020a; Orellano et al., 2017; Mortimer et al., 2008; Jedrychowski et al., 2010; Morales et al., 2015; Lee et al., 2018a; Bougas et al., 2018; Cai et al., 2020; Hehua et al., 2017; Lavigne et al., 2018; Lee et al., 2018b; Sbihi et al., 2017; Fuertes et al., 2015; Gehring et al., 2013; Agier et al., 2019; Wallas et al., 2020; Fuertes et al., 2020b; Parmes et al., 2020; Gascon et al., 2016). Air pollution exposure after birth is suggested to be associated with lower lung function (Garcia et al., 2021), increased risk of wheezing and asthma (Khreis et al., 2017; Gehring et al., 2020; Fuertes et al., 2020a), and exacerbating both pre-existing conditions (Orellano et al., 2017) during childhood. Previous studies examining the role of maternal exposure to air pollution during pregnancy on child's respiratory health reported mixed findings (Fuertes et al., 2020a; Mortimer et al., 2008; Sbihi et al., 2017; Fuertes et al., 2015; Gehring et al., 2013; Agier et al., 2019; Jedrychowski et al., 2010; Morales et al., 2015; Lee et al., 2018a; Bougas et al., 2018; Cai et al., 2020; Hehua et al., 2017; Lavigne et al., 2018; Lee et al., 2018b). Some studies found that maternal exposure to air pollution during pregnancy was associated with lower lung function (Mortimer et al., 2008; Jedrychowski et al., 2010; Morales et al., 2015; Lee et al., 2018a; Bougas et al., 2018; Cai et al., 2020), and increased risk of wheezing (Hehua et al., 2017) and asthma in children (Hehua et al., 2017; Lavigne et al., 2018; Lee et al., 2018b; Sbihi et al., 2017), while others did not (Fuertes et al., 2020a; Cai et al., 2020; Fuertes et al., 2015; Gehring et al., 2013; Agier et al., 2019). The potential adverse health effects of other exposures related to the urban environment such as noise (Agier et al., 2019; Wallas et al., 2020), lack of green (Agier et al., 2019; Fuertes et al., 2020b) and blue spaces (Agier et al., 2019; Parmes et al., 2020), increased built environment (Agier et al., 2019), and especially the concurrence of these exposures (Agier et al., 2019) on respiratory health is limited and inconsistent (Gascon et al., 2016). Only one previous study has assessed maternal exposure to an extensive number of exposures related to the urban environment (i.e., air pollution, natural spaces, noise, built environment, traffic) during pregnancy and observed no association with child's lung function but did not study wheezing or asthma as outcomes (Agier et al., 2019). Evaluating the impact of the urban environment on respiratory health is essential as half of the global population is currently living in urban settings, and this proportion is expected to increase up to 70% by 2050 (United NationsDepartment of Economic and Social Affairs, 2018). Despite that urban living offers opportunities for a healthy living including access to services and goods, employment and social interaction, it may also imply increasing exposure to a harmful environment (Rao et al., 2007). Exploring the urban environment as a whole in relation to respiratory health, especially in vulnerable developing periods of life, may help to identify harmful urban environments to ultimately identify effective prevention strategies to reduce them. We hypothesised that the urban environment during pregnancy may play a role in the development of the respiratory and immune systems that may affect respiratory health during childhood, Therefore, we aimed to examine the associations of exposure to the urban environment during pregnancy, including air pollution, noise, traffic, green and blue spaces, and built environment with lung function, preschool wheezing, and school-age asthma among 5624 children participating in a population-based prospective cohort study.

2. Methods

2.1. Design

The present study was embedded in the Generation R Study, a population-based prospective birth cohort study in Rotterdam, the Netherlands. Pregnant women were recruited during pregnancy at their health care centers between 2002 and 2006 (Jaddoe et al., 2012). The study was approved by the Medical Ethical Committee of the Erasmus MC, University Medical Centre in Rotterdam. Written informed consent was obtained from all participants. A total of 5624 mother-child pairs were included in the current study (Fig. S1).

2.2. Urban environment during pregnancy

The range of urban environment variables was estimated at the home address during pregnancy using geographic information systems (GIS) modelling. We included a total of 30 exposures from the following exposure groups: air pollution (n = 11), road traffic noise (n = 2), traffic (n = 1), green spaces (n = 5), blue spaces (n = 2), and built environment (n = 9) (Table 1). Complete details on the exposures assessed, distributions, and data sources for the estimations are fully described in Supplementary Table S1 and Pearson correlations between all exposures in Fig. S2.

2.3. Child's respiratory outcomes

Lung function was measured at a mean age of 9.79 years (standard deviation (SD): 0.35 years) by spirometry following the American Thoracic Society and European Respiratory Society guidelines (Miller et al., 2005). We measured forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and mid-expiratory flow ($FEF_{25–75\%}$) and converted these into age-, height-, sex-, and ethnicity-adjusted z-scores (Quanjer et al., 2012). Z-scores indicate the change in standard deviations a measured value is from the predicted according to age, height, sex, and ethnicity (Stanojevic et al., 2013). Children with ≥1 acceptable manoeuvre were included in the analyses. Preschool wheezing and school-age asthma were assessed from parental-reported questionnaires adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) (Asher et al., 1995). Preschool wheezing was assessed from having had any wheezing from birth until the age of 5 years. This was assessed from a question of having had wheezing in the

Table 1
Summary of urban environmental exposures.

Exposure family	Exposure
Air pollution	NO_2, NO_x, PM_{10}, $PM_{2.5}$, $PM_{2.5absorbance}$, PM_{coarse}, $PM_{2.5}$ elemental components (Cu, Fe, K, Si, Zn)
Noise	Lden, Ln
Traffic	Inverse distance to the nearest road
Green spaces	NDVI (within 100 m, 300 m, 500 m buffer), size of nearest major green space (>5000 m^2), distance to the nearest major green space (>5000 m^2)
Blue spaces	Size of the nearest major blue space (>5000 m^2), distance to the nearest major blue space (>5000 m^2)
Built environment	Population density, building density (within 100 m, 300 m, 500 m buffer), street connectivity within 300 m buffer, facilities density within 300 m buffer, facilities richness within 300 m buffer, Land Use Mix (Shannon's Evenness Index) within 300 m buffer, Walkability within 300 m buffer

Estimated using geographic information system within PostgreSQL (copyright © 1996–2017 The PostgreSQL Global Development Group), PostGIS (Creative Commons Attribution-Share Alike 3.0 License http://postgis.net), Python (Python Software Foundation. Python Language Reference, version 2.7. Available at http://www.python.org) and R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) platforms.

past 12 months (yes, no), which was annually asked at the ages of 1–5 years. At a mean age of 9.79 years, school asthma was defined as ever-physician-diagnosed asthma with either wheezing or asthma medication use in the past 12 months.

2.4. Covariates

Maternal characteristics were obtained from questionnaires during pregnancy and included highest educational level finished (low: no education, primary school, secondary school or intermediate vocational training; high: university degree or higher vocational training), age at pregnancy (years), pre-pregnancy body mass index (BMI; kg/m^2), smoking during pregnancy (yes; no), and history of asthma and atopy (ever been diagnosed, yes; no). Additionally, information on area-level SES was obtained from the Social and Cultural Planning Office of The Netherlands. Area-level SES was assessed as quintiles of the neighbourhood deprivation, considering education, income, and position on the labour market of the neighbourhood inhabitants. Child's sex (female; male), gestational age at birth (weeks), and birth weight (g) information was collected from midwife and hospital records at birth. Child's height (cm) was measured at the time of the lung function assessment and ethnicity information (caucasian, african/american, south east asian, north east asian, other/mixed) was assessed by country of birth from parents and grandparents from questionnaires. Covariates were selected from literature and summarised in a directed acyclic graph (DAG) to depict the known and hypothesised causal relations between variables and avoid adjusting for mediators or colliders (Fig. S3).

2.5. Statistical analysis

We performed a non-response analysis comparing mothers and children included in the analyses to those lost to follow up at the age of 10 years using chi-square tests for categorical variables and independent samples t-tests for continuous variables. Multiple imputation by chained equations (White et al., 2011) was performed for missing values in exposures and selected covariates. All variables not following a normal distribution were transformed to approach normality. A total of 10 imputed datasets were generated and Rubin's rules were applied to summarise effect estimates (White et al., 2011). We standardised by the interquartile range (IQR) of all continuous exposures to ensure comparability of exposure estimates. Therefore, all continuous exposure estimates are expressed as IQR increase (equivalent to passing from the 25th to the 75th percentile). Because area-level SES may play a substantial role in the association between the urban environment and childhood respiratory outcomes, we standardised all exposures by the mean exposure level in each quintile of area-level SES to reduce any residual confounding.

We examined associations of the urban environment during pregnancy with lung function, preschool wheezing, and school-age asthma using two complementary approaches. As a first exploratory analysis, we performed a descriptive screening of single exposure-outcome associations with an exposome-wide association study (ExWAS). The ExWAS assessed the associations through multivariable linear (for lung function) or logistic (for wheezing and asthma) regression models and was corrected for multiple testing using an adapted version of the Bonferroni correction that takes into account the correlation structure of the data (corrected p-value = 0.003) (Li et al., 2012). Estimates for lung function models are expressed as z-score change and for wheeze and asthma models as odds ratio (OR). Second, to assess the associations closer to a real-life scenario because populations are simultaneously exposed to numerous urban environmental exposures, we applied a hierarchical clustering on principal components (HCPC) analysis to identify children sharing similar urban exposure patterns. This was considered the main analysis. We first applied a principal component analysis (PCA) to reduce the data dimension and retained the components that explained at least 90% of the variance (Table S2). We applied an ascending hierarchical classification based on the PCA components to identify clusters of exposure (Fig. S4). Then we used the identified clusters as the independent variable in the linear and logistic regression models. Models from both approaches were adjusted for a common set of covariates selected from the DAG (Fig. S3). Lung function models were adjusted for maternal education, pre-pregnancy BMI, age, smoking during pregnancy, history of asthma or atopy, and child's ethnicity and season of birth. Wheezing and asthma models were additionally adjusted for child's sex.

Further sensitivity analyses were performed to assess the robustness of the results. We described the levels of urban exposures and distribution of outcomes in each area-level SES strata. Lung function models were repeated including only children with 3 acceptable and reproducible manoeuvres from the spirometry test. We further repeated the cluster analyses excluding children born preterm or with a low birth weight, assessing preschool wheezing considering wheeze presenting at only 1 or at 2 or more ages from age 1–5 years, and assessing wheezing separately at every age from age 1–5 years. Statistical analyses were performed using R Statistical Software version 3.6.1.

3. Results

Subject characteristics Maternal and child characteristics are shown in Table 2. Maternal exposures are shown in Table S1. Briefly, median (IQR) pregnancy air pollution levels (e.g., NO_2 = 38.48 (7.48) μg/m^3, $PM_{2.5}$ = 19.72 (3.83) μg/m^3) were above the 2021 WHO air quality guidelines (10 μg/m^3 for NO_2, 5 μg/m^3 for $PM_{2.5}$). Of all mothers, 52% were exposed to daily road traffic noise levels above the current WHO recommendations (Lden>53 dB). Non-response analyses showed that children included in the analyses had mothers who were older, with lower pre-pregnancy BMI, higher education, and living in less deprived neighbourhoods compared to those lost at follow up at the age of 10 years. Children included in the analyses were less likely to be born preterm or with a low birth weight and were less ethnically diverse (Table S3). There were no differences in maternal and child characteristics between the complete case and the imputed datasets (Table S4).

3.1. Urban environment during pregnancy and child's respiratory outcomes

3.1.1. Single exposure analyses

Higher exposure to PM was related to higher FEV_1 (z-score change for $PM_{2.5}$: 0.05 [0.02, 0.08], PM_{10}: 0.04 [0.01, 0.07]; PM_{coarse}: 0.04 [0.01, 0.07]) and FVC ($PM_{2.5}$: 0.06 [0.03, 0.08], PM_{10}: 0.05 [0.02, 0.08]; PM_{coarse}: 0.04 [0.01, 0.07]), and lower $FEF_{25–75\%}$ ($PM_{2.5}$ and PM_{10}: −0.06 [−0.09, −0.03], $PM_{2.5abs}$: −0.03 [−0.07, 0.00]; PM_{coarse}: −0.03 [−0.06, 0.00]) (Table S5). Higher exposure to NO_2 was associated with lower $FEF_{25–75\%}$ (−0.04 [−0.07, 0.00]) (Table S5), and nitrogen oxides with higher odds of preschool wheeze (OR for NO_2 and NO_x: 1.08 [1.01, 1.16]) (Table S6). Higher size of the nearest major blue space was associated with higher FEV_1 (0.04 [0.01, 0.06]) and FVC (0.03 [0.00, 0.05]), and lower odds of school-age asthma (0.87 [0.75, 0.99]). Indicators of urbanicity (i.e., exposures from the built environment) were associated with lower lung function and higher odds of preschool wheezing (e.g., street connectivity with lower FEV_1 [−0.03 (−0.06, 0.00)], and facilities density (e.g., schools, medical centers, shops) with higher wheezing [1.07 (1.01, 1.14)]; Tables S5–S6). However, after correction for multiple testing (p = 0.003), only the associations of higher $PM_{2.5}$ with higher FEV_1, FVC and lower $FEF_{25–75\%}$, higher PM_{10} with higher FVC and lower $FEF_{25–75\%}$, and higher PM_{coarse} with higher FVC remained statistically significant.

3.1.2. Cluster analyses

We obtained 3 different clusters of the urban environment (Fig. 1). Cluster 1 (n = 1598) identified mother-child pairs exposed to lower levels of air pollution, road traffic noise, traffic, and urbanisation, in

Table 2
Maternal and child characteristics.

	Population for analysis (n = 5624)
Maternal characteristics	
Age (years)	31.00 (4.92)
Pre-pregnancy BMI (kg/m2)	23.47 (4.10)
Education, low	2550 (49%)
Smoking	
Never	3784 (77%)
Before pregnancy	429 (9%)
During pregnancy	727 (15%)
History of asthma or atopy, yes,	1804 (37%)
Area-level SES	
Quintile 1, least deprived	593 (11%)
Quintile 2	646 (12%)
Quintile 3	663 (12%)
Quintile 4	616 (11%)
Quintile 5, most deprived	3087 (55%)
Child characteristics	
Sex, female	2822 (50%)
Gestational age at birth (weeks)	40.14 (1.86)
Preterm birth (<37 weeks)	260 (5%)
Birth weight (g)	3450.00 (690.00)
Low birth weight (<2500 g)	239 (4%)
Season of birth	
Spring	1333 (24%)
Summer	1516 (27%)
Autumn	1541 (27%)
Winter	1234 (22%)
Ethnicity	
Caucasian	4355 (79%)
African/American	402 (7%)
South East Asian	195 (4%)
North East Asian	137 (2%)
Other/Mixed	406 (7%)
Age (years)	9.79 (0.35)
Height (cm)	141.52 (6.60)
FEV_1 (z-score)	0.16 (0.98)
FVC (z-score)	0.20 (0.94)
FEV_1/FVC (z-score)	−0.10 (0.96)
$FEF_{25–75\%}$ (z-score)	0.45 (1.09)
Preschool wheezing	1865 (37%)
School asthma	268 (6%)

Values are mean (SD) for continuous variables and N (%) for categorical variables.

Abbreviations: BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1s; $FEF_{25–75\%}$: mid expiratory flow; SD: standard deviation.

terms of population density, building density, and walkability, and to higher levels of green and blue spaces. We selected this cluster as the reference cluster in our analyses because it had the lowest levels of a priori harmful exposures. Cluster 2 (n = 2835) was characterised by lower levels of air pollutants and noise, higher distance to natural spaces, more densely population and built areas, and less diversity in land use. Cluster 3 (n = 1191) identified mother-child pairs who were exposed to higher air pollution and noise, and lived in more walkable areas, with lower exposure to green and blue spaces. Mother-child pairs between clusters differed in terms of maternal age, pre-pregnancy BMI, education, and child season of birth, ethnicity, and rates of preschool wheezing (Table S7). Most prominently, compared to Cluster 1, children belonging to Cluster 3 had lower $FEF_{25–75\%}$ (−0.08 [−0.17, 0.00]) and higher odds of preschool wheezing (1.21 [1.03, 1.43]). We did not observe associations of Cluster 3 with FEV_1, FVC, FEV_1,/FVC nor with school-age asthma and neither of Cluster 2 with any respiratory outcome (Table 3).

3.1.3. Sensitivity analyses

We observed differences in the distributions of exposures across SES strata without a clear pattern of harmful or beneficial exposures across quintiles of SES (Table S8). The observed associations remained materially similar when we included only children with reproducible spirometry measurements (Tables S9–S10), and when excluding preterm and low weight born children (Table S11). The observed effect estimates for the associations of urban exposure clusters with preschool wheezing were similar when assessing wheezing presenting at only 1 age or at ≥2 ages from age 1–5 years as the outcomes. We did not observe associations at any specific age separately although a tendency for higher odds for associations of urban exposure clusters with preschool wheezing ate age 2 years was observed (Table S12).

4. Discussion

This study is one of the first that systematically analysed multiple urban exposures in relation to child's respiratory health and described three patterns of urban exposures during pregnancy in an urban setting in The Netherlands. This study showed that higher exposure to particulate matter during pregnancy was associated with lower lung function in mid-to-small airways. This study also showed that living during pregnancy in an urban environment characterised by higher levels of air pollution, noise, walkability, street connectivity, and lower levels of natural spaces contributes to lower lung function in mid-to-small airways, and to increased odds of preschool wheezing.

4.1. Comparison with previous studies

We considered a wide range of urban exposures to create clusters of exposures and we observed that compared to mother-child pairs living in less polluted, less noisy, more natural, and less urban areas, those living in more walkable areas with higher air pollution and noise, and lower levels of green and blue spaces had lower $FEF_{25–75\%}$ and increased odds of preschool wheezing. We did not observe notable associations with those living in areas with lower levels of air pollution, noise, natural spaces, and higher levels of urbanisation with respiratory outcomes. This suggests that lower levels of air pollution alone might not be enough and highlights the importance of the existence of urban settings that are characterised by lower traffic-related air pollution, lower urbanisation (i.e., lower building and population density or street connectivity), and higher volume of areas with natural spaces simultaneously for a better respiratory health of children. To our knowledge, only one study had previously considered a wide range of urban exposures during pregnancy in relation to lung function (Agier et al., 2019), but not with wheezing and asthma in childhood. In that study, authors did not find any association with lung function in single or multiple-exposure analysis. They only reported a positive association with inverse distance to the nearest road, considered a spurious finding. In that study, the statistical power was limited to assess the multiplicity of the exposures included with the small effect on lung function that was expected. Differences in findings with our study might also be explained by non-differential exposure misclassification due to measurement error that might have attenuated the effect estimates (Agier et al., 2019).

Most previous studies used single-exposure approaches that do not account for the complex interrelationship of the multiple environmental exposures that are present in an urban setting. Our results from the single-exposure analysis confirm the adverse effects of air pollution on mid-to-small airways (Mortimer et al., 2008; Morales et al., 2015; Bougas et al., 2018), and on the risk of early childhood wheezing (Hehua et al., 2017; Chen et al., 2022) observed in previous studies and in our findings in cluster analysis. However, in single-exposure analyses we observed an association of higher prenatal exposure to particulate matter with higher FEV_1 and FVC, which was not present in the cluster analysis. These contradictory results add to the current inconsistent evidence (Mortimer et al., 2008; Jedrychowski et al., 2010; Lee et al., 2018a; Cai et al., 2020; Fuertes et al., 2015; Gehring et al., 2013; Agier et al., 2019), highlight the importance of considering air pollution within the complexity of urban exposures and should be further explored before any strong conclusions can be made. Of importance, our findings highlight the relevance of $FEF_{25–75\%}$ as an early marker of small airways impairment (Marseglia et al., 2007).

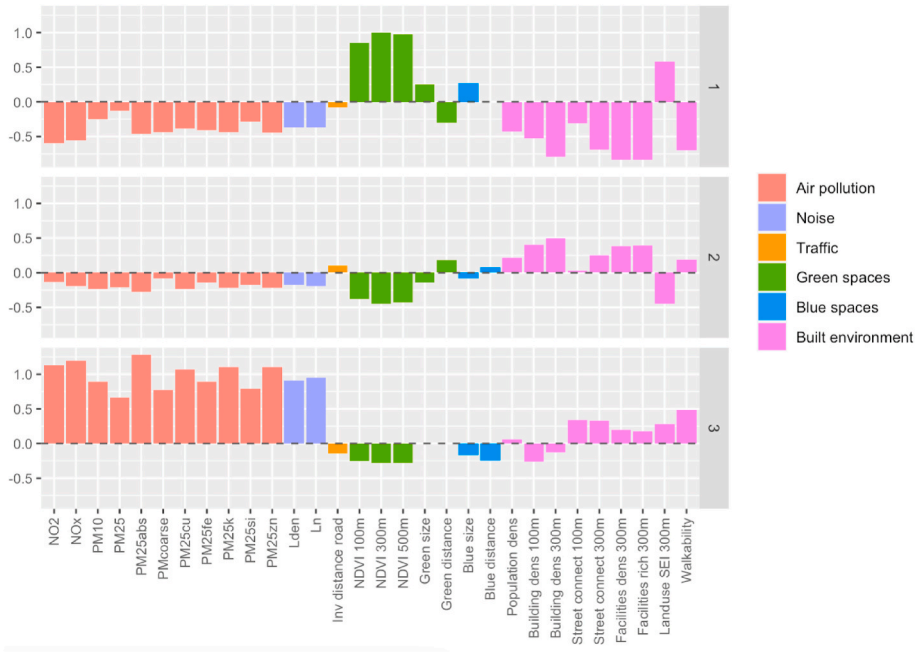

Fig. 1. Description of the clusters of maternal exposure during pregnancy to the urban exposures.
Bars represent the level of exposure of each urban exposure in the cluster compared to the mean level of exposure in the overall population (mean = 0).

Table 3
Associations of maternal exposure during pregnancy to the urban environment in clusters and lung function, preschool wheezing, and asthma in school-age children.

	Maternal exposure to clusters of urban environment		
	Cluster 1 (n = 1598) [a]	**Cluster 2 (n = 2835)** [a] Estimate (95% CI)	**Cluster 3 (n = 1191)** [a] Estimate (95% CI)
Lung function (z-score change)	*Reference*		
FEV_1		−0.02 (−0.08, 0.05)	−0.03 (−0.11, 0.05)
FVC		−0.01 (−0.07, 0.05)	−0.02 (−0.09, 0.06)
FEV_1/FVC		0.00 (−0.06, 0.06)	−0.03 (−0.11, 0.05)
$FEF_{25–75\%}$		−0.02 (−0.09, 0.05)	−0.08 (−0.17, 0.00)
Wheezing and asthma (OR)	*Reference*		
Preschool wheezing		1.13 (0.98, 1.29)	1.21 (1.03, 1.43)
School asthma		1.22 (0.91, 1.65)	1.02 (0.70, 1.48)

[a] Cluster 1 (reference) identified mothers during pregnancy exposed to lower levels of air pollution, road traffic noise, traffic, and urbanisation, in terms of population density, building density, and walkability, and to higher levels of green and blue spaces, cluster 2 those exposed to lower levels of air pollutants and noise, higher distance to natural spaces, more densely population and built areas, and less diversity in land use, and cluster 3 those exposed to higher air pollution and noise, and lived in more walkable areas, with lower exposure to green and blue spaces. Lung function models were adjusted for maternal education, pre-pregnancy BMI, age, smoking during pregnancy, history of asthma or atopy, and child's ethnicity and season of birth. Preschool wheezing and school asthma models were additionally adjusted for child's sex. Abbreviations: FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; $FEF_{25–75\%}$: mid expiratory flow; OR: odds ratio; CI: confidence interval.

Previous studies that assessed noise exposure during pregnancy reported null associations in relation to wheezing and asthma until adolescence. Considering the prevalent high noise exposure and our findings, early life exposure to noise in relation to child's respiratory health merits further investigation. Living in less natural (green and blue) areas was detrimental for children's lung health. In line with our results, the scarce available evidence shows a potential beneficial effect of green spaces (Fuertes et al., 2020b). Our study is the first to report an association between blue spaces and respiratory health, observed in cluster and single-exposure analyses. Only one study previously assessed prenatal exposure to blue spaces in relation to lung function and reported null associations (Agier et al., 2019). However, the levels of blue spaces in that study were very low and were only assessed as presence or absence of blue spaces in a 300 m buffer (Agier et al., 2019). The Rotterdam area is a unique setting with very high proportion of blue spaces (including a river, lakes, canals, and an extensive industrial port), compared to other cities. Given the potential health benefits of blue spaces, but at the same time the risks of the industrial port, further research is guaranteed. We observed that a built environment with higher street connectivity, facilities, and walkability, when assessed in combination with other urban exposures, was related to worse respiratory health. Contrary to the only study that has assessed the influence of the built environment during pregnancy on childhood respiratory health so far (Agier et al., 2019), which reported no associations with lung function.

Every urban environment is unique in terms of its urban features and demographic characteristics, thus, our results need to be interpreted in view of its specific urban setting. Rotterdam, with an extension of 324 km^2, is the second largest city in the Netherlands with 663,900 inhabitants and one of the most densely populated in the country with 3040 inhabitants/km^2 as of 2023 (Centraal Bureau voor de Statistiek, 2023a). It comprises a large number of green and blue spaces as well as an extensive cycling network, including a length of 117 km of cycling network per 100 km of motorway (Centraal Bureau voor de Statistiek, 2023b). In socioeconomic terms based on the city's mean levels of prosperity, education, and employment, Rotterdam ranks among the lowest in The Netherlands (Centraal Bureau voor Statistiek, 2023). Higher socioeconomic deprivation has been consistently associated with worse health outcomes (Kivimäki et al., 2020). However, the way how SES influences the associations of urban exposures with health is not clear, it can be non-linear, and is context specific (Sum et al., 2022). Similarly, the association between socioeconomic deprivation and

patterns of urban exposures is unclear and context specific. While in the US studies have shown an association of higher deprivation with exposure to more harmful environments, in the EU findings have been mixed (Hajat et al., 2015). In our study population, levels of exposure across SES quintiles were mixed. Because of that, we thoughtfully adjusted our models for the relevant individual-level SES covariates and we further standardised the exposures by area-level SES. Given the complexity and uniqueness of urban scenarios in terms of the coexistence of potentially beneficial and detrimental exposures, more studies integrating many urban exposures in the context of socioeconomic factors in different urban settings are needed.

4.2. Interpretation of results

Our study is based on the Developmental Origins of Health and Disease (DOHaD) hypothesis, which posits that exposures during critical periods of development, particularly during pregnancy, can influence long-term health outcomes (Barker, 2007). During pregnancy, the lungs undergo crucial phases of formation and development and are especially vulnerable to environmental exposures (Miller and Marty, 2010). Exposures during pregnancy may lead to adaptations and alterations in the development that could manifest as long-term health effects, as in alterations in lung function or manifestations of wheeze and asthma symptoms during childhood.

In our study we observed that living during pregnancy in an urban environment characterised by higher levels of air pollution, noise, walkability, street connectivity, and lower levels of natural spaces contributes to a lower lung function in mid-to-small airways, and to higher odds of preschool wheezing, but not with school age asthma. Preschool wheezing is a respiratory symptom that may also represent a different aetiology than childhood asthma. Preschool wheezing may be triggered by a myriad of factors, including viral infections, which are prevalent in this younger age group. Repeated wheezing episodes before the age of 5 may not necessarily progress to a persistent asthma phenotype, which is consistent with the lack of associations observed with school-age asthma. The urban environment during pregnancy may alter the development of the immune system making younger children more susceptible to respiratory infections.

Air pollutants inhaled by the mother during pregnancy can cross the placenta and thus have a direct effect on the foetus development (Bové et al., 2019). Oxidative stress, inflammation, and epigenetic changes are suspected to play an important role on the respiratory effects of air pollution (Lee et al., 2018a; Thurston et al., 2020) as well as disrupting the hypothalamic-pituitary-adrenal (HPA) axis (Thomson, 2019). Early life air pollution exposure has been linked to lower club cell secretory protein (CC16) levels in childhood, which in turn is associated with decreased lung function (Beamer et al., 2019; Stapleton et al., 2022). Air pollution could directly affect lung development by disturbing organogenesis due to the aforementioned mechanisms, and indirectly affect it through adverse birth outcomes.

Noise acts as a physiological and psychological stressor. It is suggested to promote stress responses through the HPA axis leading to the release of stress hormones such as cortisol (Recio et al., 2016). Maternal psychological distress during pregnancy has been associated with preschool wheezing (Guxens et al., 2014), and lower lung function and asthma at school-age (Van Meel et al., 2020). Stress mechanisms may also disrupt sleep and night-time recovery of the immune system, leading to inflammatory processes also in the respiratory system (Recio et al., 2016). Further, chronic stress-reactions and sleep disturbances may lead to alterations in the endocrine system that could impair critical developmental processes of the lung and immune system (Recio et al., 2016; Schmidt et al., 2013). Green and blue spaces could act as mitigators of harmful exposures such as air pollution (Heo and Bell, 2019). Exposure to green spaces around the home has been associated with reduced serum IgE levels in children, which is a biomarker of asthma and bronchial hyperresponsiveness (Ruokolainen et al., 2015). Also, they could have a beneficial effect by promoting healthier lifestyles, reducing stress (e.g., increasing physical activity, promoting social cohesion) (van den Bosch et al., 2017), or by influencing individual's microbiome as postulated by the biodiversity hypothesis (Prescott, 2020). The features of the built environment can influence on the magnitude of environmental stressors and on health-related behaviors (Nieuwenhuijsen, 2016). Although in The Netherlands the use of active transportation (i.e., cycling) is common, more efforts can be put into developing an even more pedestrian or active transportation focused and naturalized design in detriment of traffic. That would lead to less traffic-related air pollution and increased physical activity in the population, that consequently would provide beneficial health effects.

4.3. Strengths and limitations

The strengths of this study are its population-based design with a large sample size and its assessment with complementary approaches to assess the complexity of a wide range of urban environment exposures in relation to multiple outcomes across childhood. This might help avoid publication bias compared to single-exposure approaches. To our knowledge, this is the first study to comprehensively assess a wide range of urban environment exposures on wheeze and asthma in addition to lung function outcomes in children. We used the HCPC method for multiple exposure assessment, which allowed us to identify patterns of urban exposures by reducing the dimensionality while dealing with the correlation structure of the exposure dataset, facilitated the interpretation of the urban exposures and respiratory health outcomes, and reduced the problem of multiple testing (Santos et al., 2020). However, we acknowledge there are other multiple-exposure assessment approaches such as variable selection and dimension reduction methods (Santos et al., 2020; Warembourg et al., 2023). Also, we acknowledge that the identified patterns of exposure are study area specific, which merits future validation of our results in other urban settings. Further, lung function was assessed with spirometry following the ATS/ERS guidelines and performed by trained research staff, which provided objective and reliable measurements. Some methodological limitations need to be addressed. First, results for $FEF_{25–75\%}$ need to be interpreted with caution as it is a parameter with high variability, especially in children. However, in sensitivity analyses, when we included only children with reproducible spirometries, results remained robust. Second, in approaches examining a broad range of exposures, measurement error bias is present in a different magnitude across exposures. Thus, the comparison of each exposure associations with respiratory health should be interpreted cautiously. Third, although we examined exposure-by-exposure associations as well as simultaneous exposures identifying patterns of exposures in the cluster analysis in an attempt to get closer to a real-life scenario, we did not assess possible effect modification nor mediation between co-occurring exposures because the complete interrelationship between all co-occurring exposures in an urban environment is not yet fully understood and there is yet no consensus on the best methodological approach. Last, we focused our study to exposures occurring during pregnancy because of the relevance and potential long-term health implications of exposures occurring in that period. However, we did not add exposures occurring during childhood to prevent more layers of complexity into the already highly advanced models leading to difficulties in interpretation of findings. Nevertheless, we consider childhood also as a relevant period of development and exposures occurring during such period could have important implications and potential to modify health effects initiated during prenatal development. Further studies are needed to address the complexity of cumulative prenatal and childhood exposures to carefully explore individual effects in critical age windows, which would hold significant public health implications for the development of mitigation strategies tailored to specific life stages.

5. Conclusion

In conclusion, this study shows that the urban environment during pregnancy is of relevance to the offspring's respiratory health in childhood. Thus, improving the urban design to minimise harmful and maximise beneficial urban exposures, along with reducing social inequalities related, is key to ensure a healthy respiratory development in childhood, that in turn, will result in a reduction of respiratory morbidity later in life.

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CRediT authorship contribution statement

Alicia Abellan: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Investigation, Methodology. **Charline Warembourg:** Formal analysis, Methodology, Writing – review & editing. **Sara M. Mensink-Bout:** Data curation, Writing – review & editing. **Albert Ambros:** Data curation, Writing – review & editing. **Montserrat de Castro:** Data curation, Writing – review & editing. **Serena Fossati:** Writing – review & editing. **Mònica Guxens:** Funding acquisition, Writing – review & editing. **Vincent WV. Jaddoe:** Funding acquisition, Writing – review & editing. **Mark J. Nieuwenhuijsen:** Methodology, Writing – review & editing. **Martine Vrijheid:** Conceptualization, Writing – review & editing. **Susana Santos:** Conceptualization, Methodology, Writing – review & editing. **Maribel Casas:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing, Methodology, Validation. **Liesbeth Duijts:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123345.

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