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Holistic evaluation of the impact of pregnancy urban exposome on infant wheezing and chest infections: an outcome-wide approach☆

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ABSTRACT

Background: Few studies have considered the complex interplay of the urban exposome in association with multiple respiratory outcomes during infancy.
Aim: Utilizing an outcome-wide exposome approach, we aimed to assess associations of pregnancy urban exposome with offspring wheezing and chest infections at different time points within the first 18 months of life.
Methods: The analysis included data from 1032 mother–child pairs from the Barcelona Life Study Cohort (BiSC) (2018–2021). In total, 44 urban exposome factors were assessed during pregnancy, including air pollution, noise, temperature, humidity, green and blue spaces, and socioeconomic and lifestyle factors. Wheezing and chest infection were evaluated simultaneously at 2, 6, 12, and 18 months. We applied mixed-response sparse reduced-rank regression (MsRRR), with resampling procedures, adjusting for potential confounders. This many-to-many modelling approach identifies exposures concurrently associated with multiple interrelated outcomes.
Results: We found 13 exposures consistently associated with wheezing and chest infection across four time-points. Maternal education was the most consistent protective factor with odds ratios (OR) ranging from 0.65 to 0.81 for university and 0.88 to 0.96 for secondary education (vs. primary education) (all $p < 0.05$). Other important

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protective factors were size of nearest green space and maternal light-intensity physical activity. NO_2 (OR 1.02–1.08), outdoor temperature (OR 1.02–1.04), and noise annoyance (OR 1.01–1.03) were consistently associated with increased risk. Area-level socioeconomic status indicators showed inverse associations.
Conclusion: Pregnancy urban exposome may influence both wheezing and chest infections in infancy. Identifying key determinants through an outcome-wide exposome approach can inform targeted public health interventions towards more holistic urban planning strategies.

1. Introduction

Urban living can foster healthier lives by offering improved access to healthcare and education facilities and better economic opportunities, while also presenting challenges such as increased exposure to deleterious environmental factors, sedentary lifestyle, and higher inequality (Nieuwenhuijsen, 2016). Urban-related environmental exposures such as air pollution, noise, temperature and urban spaces including green, blue and grey spaces have been associated with a wide range of health outcomes, including respiratory diseases (Jacquemin et al., 2015; Johannessen et al., 2023; Tischer et al., 2018; Maio et al., 2022; Gascon et al., 2017). While consistent evidence, though varying in strengths, links air pollution, noise, and temperature variations to the development and worsening of lung diseases (Jacquemin et al., 2015; Maio et al., 2022; Recio et al., 2016), evidence on green spaces is currently mixed, with some studies suggesting beneficial associations and others indicating potential adverse effects through various mechanisms (Johannessen et al., 2023; Gascon et al., 2017).

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, the pregnancy period is a critical window of susceptibility during which environmental exposures may induce long-term biological adaptations or developmental alterations (Barker, 2007; Abellan et al., 2024; Garcia et al., 2021; Gascon et al., 2016). Disruptions during fetal development may impair lung maturation and immune system function, predisposing infants to early adverse respiratory outcomes, which are clinically significant and could serve as indicators of future respiratory morbidity (Wright, 2010; Kallapur et al., 2019). Previous studies have shown that early life respiratory infections and wheezing are associated with a higher risk of developing chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) and contribute to reduced lung function in adulthood (Gehring et al., 2020; Grant et al., 2020).

Most existing epidemiological evidence investigating urban environmental exposures has predominantly focused on single or a limited set of exposure factors, when in reality populations are concurrently exposed to a complex mixture of environmental factors (Stafoggia et al., 2017). To tackle this, an exposome approach has been developed, taking into consideration the totality of exposures individuals experience (Wild, 2012). The exposome approach is a more holistic approach that capture the wide spectrum of environmental factors a person is exposed to from conception onward (Wild, 2012; Buck Louis et al., 2017; Wild, 2005). In the context of urban environments, this has given rise to the concept of urban exposome, referring to the multi-dimensional set of exposures individuals encounter in urban settings, including physical and chemical factors, as well as social determinants and lifestyle (Morawska et al., 2019; Andrianou and Makris, 2018). Applying this concept to environmental health research has provided an opportunity to investigate the impact of multiple exposures simultaneously, offering a more comprehensive understanding of how complex exposure mixtures influence health outcomes.

The exposome approach has unleashed the development of new statistical approaches to deal with the complex exposome data. In this context, novel outcome-wide analytical exposome approaches have been developed where the impact of a single exposure (within a mixture of exposures) is simultaneously assessed on multiple interrelated outcomes (i.e. studying many-to-many associations) (VanderWeele, 2017; Anguita-Ruiz et al., 2023). These approaches allow researchers to investigate how an exposure impacts multiple health outcomes within the same analytical framework, which can reduce bias from mediation and collider stratification by avoiding adjustment of downstream variables (VanderWeele, 2017; Steptoe and Fancourt, 2020; VanderWeele et al., 2020). Additionally, these approaches are particularly valuable for policymaking where understanding the wider impact of a specific exposure across many outcomes could be helpful in prioritizing public health recommendations (VanderWeele, 2017).

To date, this innovative approach has been rarely applied in exposome studies, where multiple predictors are analysed collectively in relation to multivariate outcomes (Anguita-Ruiz et al., 2023; Anguita Ruiz et al., 2024) in longitudinal studies. Thus, this study utilized an outcome-wide exposome approach to comprehensively evaluate the association of urban exposome (i.e., air pollution, noise, temperature, humidity, green, blue, and grey spaces, individual- and neighbourhood-level socioeconomic status (SES), and lifestyle) during pregnancy with early-life respiratory outcomes in infants.

2. Materials and methods

This study was conducted based on data from the Barcelona Life Study Cohort (BiSC), which is an exposome cohort in the Barcelona metropolitan area, Spain. The full BiSC cohort profile is described in detail elsewhere (Dadvand et al., 2024). Briefly, participants were enrolled during the first routine pregnancy check-up (11–14 gestation weeks) between 2018 and 2021 at three major tertiary university hospitals in Barcelona. A total of 1080 women with singleton pregnancy, age range 18 to 45, residing in the catchment area, and able to communicate in Spanish/Catalan were included at baseline with follow up in the first, second and third trimester of pregnancy and postnatally (1-, 2-, 6-, 8-, 12-, 18-, 28-, and 48 months). Information collected during pregnancy includes sociodemographic characteristics, parental lifestyle, general and specific external and internal exposomes. Ethical approval was obtained from all the participating institutions and hospitals, and written informed consent was obtained from all participants prior to their enrollment in the cohort.

2.1. Outcomes

We included the two early-life respiratory outcomes available in the BiSC study, namely wheezing and chest infections, each assessed four times in the first 18 months (2, 6, 12, and 18). Data were collected using the Spanish or Catalan version of the validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, administered to parents (Carvajal-Urueña et al., 2005):

(a) Wheezing, defined as response to the question “Which of the following statements best describes your child”; never has wheezing, occasional (between 1–3 wheezing episodes) and/or recurrent (4 or more wheezing episodes). Dichotomized as “yes” for occasional and/or recurrent episodes and “no” for those who reported never having wheezing. We dichotomized to focus on the presence of any wheezing, which is a clinically meaningful threshold commonly used in epidemiological studies (Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC), 1998).

(b) Chest infection, defined as a positive response to "Has a doctor ever told you that your child had chest infection?" (yes/no)

2.2. Urban exposome assessment

A wide range of urban exposures were assessed for each mother during pregnancy using a combination of personal and home monitoring, modelling approaches, geospatial analyses, remote sensing data, and questionnaires. Exposure assessment methods are described in detail in the supplemental data (pp. 2–5) and elsewhere (Dadvand et al., 2024). We included 44 exposure variables from 6 exposure families for the pregnancy period, as detailed in Table 1 and Table S1.

2.2.1. Air pollution

A detailed description of our air pollution assessment method is published elsewhere (Domínguez et al., 2024). Briefly, we applied land use regression models to estimate nitrogen dioxide (NO_2), black carbon (BC), particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), and $PM_{2.5}$ Copper (Cu) at home, workplace, and commuting route between home and workplace. During the period of January 2021 to February 2022, three monitoring campaigns (BiSCAPE campaigns) were conducted in traffic, urban and background sites across the BiSC study area. The LUR models were developed using data collected in BiSCAPE campaigns by identifying the main predictors of air pollution (e.g., street type, greenness coverage, distance to major road, high population density, and traffic density) in accordance with the European Study of Cohorts for Air Pollution Effects (ESCAPE) guidelines (Dadvand et al., 2024). Estimates for air pollution levels were averaged over the whole pregnancy, and the total air pollution level was estimated as the average of outdoor exposure levels at home address, workplace and commuting route, weighted by the time the participants used to spend in each microenvironment.

Table 1
List of the pregnancy exposome variables assessed in this study.

	Exposure description
Air pollution (4)	NO_2, $PM_{2.5}$, Copper (Cu_pm25) content in $PM_{2.5}$, and BC.
Natural space (17)	NDVI (50, 100, and 300 m buffers), NDVI_mroad (NDVI within 50 buffer distance to major roads), NDVI_distant_mroad (NDVI distance to major roads), Urban_green (percentage of urban greenness within 50, 100, 300 and 500 m buffer), Natural_spaces_50 (natural greenspace within 50 m buffer), Distance_green_space (distance to nearest greenspace of <5000 m^2), Size_green_space (size of nearest greenspace of <5000 m^2), Distance mgreen (distance to nearest major greenspace of >5000 m^2), Size_mgreen (size of nearest major greenspace of <5000 m^2), Access_mgreen (percentage of time participant have access to major greenspace), Time_green_space (time spent in green spaces including parks, forests, garden and agricultural fields), and Time_blue_space (time spent in blue spaces)
Noise (2)	Noise_annoyance (noise from cars, train, leisure, industry, works, and other sources), and Traffic noise (noise from road traffic, l_{den}).
Meteorology (3)	Indoor temperature, indoor humidity, and outdoor temperature
Social factors (8)	Individual level: Maternal_education (maternal education including primary or less, secondary and university), and Ethnicity (European, European/Latin American, Latin American and other). Neighbourhood level: Consumption_unit (average income per consumption unit), GINI_index, Relative_poverty (population with income per consumption unit below 60 % of the median), Studying_higher_edu (percentage of people pursuing higher education out of population aged 16 and over), Completed_higher_edu (percentage of people with higher education out of population aged 16 and over), and Unemployment_rate (unemployment rate as a percentage of the active population).
Lifestyle (10)	Physical activity (activity_score, sedentary and light, moderate, and vigorous intensity exercises), Active_smoking (maternal smoking during pregnancy) and Passive_smoking (maternal exposure to cigarette smoke), Sustained_smoker (maternal sustained smoking during pregnancy), Alcohol_consumption (drinking alcohol during pregnancy), and Pets_home (having pets including dogs, cats and others in the household).

BC, black carbon; Cu, copper; NDVI, Normalized difference vegetation index; NO_2, nitrogen dioxide; PM $_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; l_{den}, day-evening-night level.

2.2.2. Noise

Standardized questionnaires on 11-point Likert scale (0–10) were used to assess source-specific (cars, train, leisure, industry, construction works, and other sources) noise annoyance. Outdoor noise levels at façades of home and workplace were derived using Strategic Noise Maps across BiSC areas that were developed under EU Directive 2002/49/EC for the period 2017–2022 (Strategic Noise Maps for urban agglomerations of Catalonia, 2021). Based on these maps, the day-evening-night (L_{den}) in dB(A) was averaged over the entire pregnancy period.

2.2.3. Temperature and humidity

Indoor temperature and humidity were measured using data loggers (EL-USB-2+, Lascar Electronics Ltd, UK) placed in participants' bedrooms for one week during the first and one week during the third trimester of pregnancy. Outdoor temperature levels for home and workplace were assessed using Random Forest models, which integrated meteorological measurements, ERA5-Land reanalysis data, and other spatiotemporal variables at a 250 m spatial resolution (Milà et al., 2023). And these measurements were averaged over the entire pregnancy period.

2.2.4. Natural spaces

The assessment of natural spaces included both urban green and blue spaces. For green spaces, various aspects were evaluated, including the surrounding green space, access to green spaces, use of green spaces, and visual access to green spaces. Normalized Difference Vegetation Index (NDVI) derived from aerial images by the Cartographic and Geology Institute of Catalonia (ICGC) at 1 m × 1 m resolution (2D indicator) was used to characterize surrounding green spaces at 50-, 100-, 300- and 500-meter buffer. NDVI values range between − 1 and 1, with higher values indicating greener spaces (a proxy of higher photosynthetic activity). Surrounding greenspace was estimated for a participant's home, workplace, and commuting route (50 m) and the total surrounding greenspace was estimated as the average of these NDVI values weighted by the time that participants used to spend in each microenvironment. Access to greenspaces was indicated as the distance to the nearest green spaces (area of <5000 m^2 and >5000 m^2) from home and workplace. Moreover, the size of the nearest green space to home and workplace was extracted as a separate exposure variable. Additionally, questionnaires were used to collect information on the use of green spaces, visual access, and time spent in green and blue spaces.

2.2.5. Social exposome

Data on individual-level SES, including ethnicity, education level, employment status, occupation, and indicators of material deprivation, were collected through face-to-face interviews and self-administered questionnaires. Neighbourhood-level (i.e., contextual) SES indicators included census-based indicators (percentage of population without university degree, percentage of population completed higher education, and percentage of unemployed people) as well as income level (based on declared income tax) at the census tract level where the participant was residing. The data on annual average household income at the census tract level was obtained from the 2020 Standard of Living and Living Conditions survey conducted by the Spanish National Institute of Statistics (INE), which is based on fiscal data including wages, pensions, unemployment benefits, other benefits, and other income, as explained in the BiSC profile article (Dadvand et al., 2024).

2.2.6. Lifestyle

Information on lifestyle factors such as active and passive smoking, alcohol consumption, as well as pet ownership before and during the current pregnancy was collected through self-administered questionnaires. Physical activity data was also objectively measured through accelerometry (ActiGraph wGT3X-BT, ActiGraph Ltd., US) for one week in the first and third trimesters, together with the Pregnancy Physical Activity Questionnaire (Coll-Risco et al., 2019) administered during the first and third trimesters.

2.3. Covariates

Maternal and children's characteristics data were obtained through questionnaires, face-to-face interviews and hospital records during pregnancy and postnatally. Selected covariates were included based on existing literature. As covariates we adjusted for child's sex (male or female), maternal specific covariates including age at pregnancy (continuous), asthma history (yes, no), parity (nulliparous, multiparous), body mass index during pregnancy (continuous) and, study period in relation to the timing of the COVID-19 pandemic (pregnancy occurring before, during, or after the start of the pandemic restrictions).

2.4. Statistical analysis

Following a test of normality, non-normally distributed quantitative variables were transformed using optimal methods, including logarithmic, square, square root, cubic, and cubic root transformations. Variables for which normality could not be achieved were dichotomized at the median (see Supplemental Table 2). Missing data (<15 %) for all exposure and adjustment variables were imputed using the "mice" package in R (Tamayo-Uria et al., 2019). The analyses were run on a single imputed dataset because the analytical approach is computationally intensive and does not readily accommodate pooling rules to penalized/dimension-reduction solutions. Similar approaches have been adopted in high dimension data or dimensional reduction methods (Tamayo-Uria et al., 2019; Kusters et al., 2022). Pearson's coefficients were used to assess the correlation structure among continuous predictors, while tetrachoric correlations were employed for binary outcomes. All continuous variables were centred and scaled to ensure comparable estimates (Anguita-Ruiz et al., 2023).

2.4.1. Main analysis

The analysis utilized mixed-response sparse reduced-rank regression (msRRR), an extension of reduced-rank regression (RRR) for outcomes of mixed types (including continuous, binary and count variables) that incorporates a feature selection step (Anguita-Ruiz et al., 2023; Anguita Ruiz et al., 2024; Luo et al., 2018). RRR assumes that all predictors and outcomes are associated through a lower-dimensional set of uncorrelated latent factors; this assumption reduces the number of estimated parameters and enhances coefficient estimation (Anguita-Ruiz et al., 2023; Izenman, 1975). RRR effectively handles multicollinearity, missing records, and multiple testing (Anguita-Ruiz et al., 2023; Chen and Huang, 2012). In addition to the latent components, the model estimates a matrix of coefficients quantifying the association between each exposure and outcome, using a binomial family with a logit link. The feature selection step incorporates a group-lasso type penalty, treating each row of the regression coefficient matrix as a group. This approach allowed coefficients for each exposure to be either completely retained or shrunk to zero, thereby selecting only relevant exposures and increasing predictive accuracy of the model (Chen and Huang, 2012). Conceptually, MsRRR has practical advantages over routine regression modelling approaches for repeated measures (e.g. mixed effects model): by modelling outcomes jointly it borrows information across correlated outcomes (increasing power and mitigating multiple testing concerns), the low rank structure stabilizes estimation under predictor collinearity, and the sparsity constraint produce compact and interpretable exposure profiles (Anguita-Ruiz et al., 2023).

In the main analysis, wheezing and chest infection time points were modelled jointly, with each time point treated as a distinct outcome, allowing for the identification of exposures simultaneously associated with each time point. Initially, the entire population was divided into training and test sets (80 % and 20 % of participants, respectively). In the training set, a 5-fold cross-validation (5-CV) was conducted to identify optimal hyperparameters, specifically, the latent components (refer to unobserved/hidden variables that capture the underlying low dimension structure linking the predictor variables and the response), and the regularization parameter (λ) which controls the weight of the penalty on model parameters. Then a model was built on the whole training set, using these hyperparameters, and predictive performance metrics were computed. This model was subsequently evaluated on the remaining 20 % test set to assess predictive performance. Lastly, after confirming no overfitting (Luo et al., 2018), a final model was built for the entire population using the identified hyperparameters for interpretation purposes. All the analyses were adjusted for a common set of confounders, including maternal age, maternal BMI, parity, maternal asthma history, COVID-19 pandemic period, and child's sex.

Since we may not always assume that the evaluated exposures influence all outcomes under study, we implemented a post-selection inference approach for the curation of outcome-wide estimates, following Anguita-Ruiz *et al.* (2023) (Anguita-Ruiz et al., 2023). We adopted the stability selection approach, a resampling-based feature selection framework, to evaluate the stability and robustness of each exposure-outcome association estimated by MsRRR. The bootstrapping procedure was fitted 500 times, and from the resulting distribution of the bootstrapped coefficient estimates, empirical *p*-values and 95 % confidence intervals (CIs) were derived for each exposure-outcome association. Due to the group-lasso penalty, the 95 %CI are typically asymmetrical, and the *p*-values obtained reflect the stability of the non-zero coefficients under resampling, i.e., the consistency with which a given predictor is retained across resamples, rather than the traditional null hypothesis significance test. Therefore, we focused on the magnitude and directionality of coefficients (β) for the interpretation of the associations. Results were presented as standardized regression β coefficients and also expressed as odds ratios (ORs) for interpretability. For binary exposures, ORs represent the change in odds of the outcome for exposed versus unexposed individuals, whereas for continuous exposures, ORs represent the change in odds per one standard deviation increase in the exposure.

2.4.2. Stratified analysis

To explore potential sex differences in the associations, the main model was stratified by offspring sex, as previous studies have shown that environmental exposures, epigenetic changes, and sex hormones can have different effects based on sex (Chowdhury et al., 2021).

To assess the robustness of our main results, we conducted a sensitivity MsRRR analysis in which wheezing and chest infection time points (2, 6, 12, and 18 months) were modelled separately rather than jointly as done in the main analysis.

All analyses were performed using R Statistical Software version 4.3.

3. Results

Table 2 presents characteristics of the participants, with a total of 1032 mothers included at birth. Mothers had a mean age of 34 year (SD 4) with pregnancy BMI of 26 (SD 4) and 56 % of them were nulliparous. 49 % of offspring were female. The proportion of children with the outcomes increased over time, with wheezing ranging from 10 % to 26 %, and chest infection ranging from 3 % to 19 % across the four-time follow-ups.

The distribution of all exposure variables in the original dataset is detailed in Table S2. Correlation coefficients between pregnancy exposure variables are shown in Fig. S1. The strongest correlations within

Table 2
Description of the study population.

	n = 1032
Maternal age (years)	34 (4)
Pregnancy BMI (kg/m^2)	26 (4)
Parity	
Nulliparous	578 (56 %)
Multiparous	454 (44 %)
Pregnancy period	
Before Covid pandemic	351 (34 %)
During Covid pandemic	310 (30 %)
After Covid pandemic	371 (36 %)
Maternal asthma history	
Yes	155 (15 %)
No	877 (85 %)
Child's sex (female)	509 (49 %)
Wheezing*	
2 months	94 (10 %)
6 months	89 (12 %)
12 months	125 (20 %)
18 months	170 (26 %)
Chest infection*	
2 months	26 (3 %)
6 months	40 (5 %)
12 months	81 (13 %)
18 months	127 (19 %)

Data are n (%) or mean (SD). *Total number of participants varied at each follow up; 2 months (n = 930), 6 months (n = 736), 12 months (n = 639), 18 months (n = 666).

exposure groups were observed among lifestyle variables (|r| = 0.74 to 0.86), social exposome variables (|r| = 0.72 to 0.84), natural space variables (|r| = 0.72 to 0.86), and air pollution variables (|r| = 0.67–0.75). Correlations across the outcome variables were mostly positive (Fig. S2). The highest correlations were observed for wheezing and chest infections assessed at the same follow-up (r 0.58–0.89). Except for the correlation of wheezing at 2 and 6 months (r = 0.29), correlations for the same outcome at adjacent follow-ups were also moderate to high (r 0.53–0.64).

3.1. Overview of the model fit

The 5-CV process identified two latent components (LCI and LC2) and a λ value of 0.9. The factor loadings of predictors and outcomes variables on the two LCs are shown in Fig. S3 and S4, respectively. Among predictors, both LCs were strongly driven by maternal education variables; however, LC2 showed smaller and more heterogeneous contributions from the other variables, suggesting a mixed contribution from some predictors (e.g. Latin American ethnicity and green space) to the overall effects in general. For the outcomes, LC1 was characterized by negative loadings across all outcomes, whereas LC2 showed a contrasting pattern, with negative loadings for wheezing and positive loadings for chest infection. Fig. S5 shows the percentage of variance in each outcome variable explained by the LCs (0.2 %–3.4 %). LC1 and LC2 together explained a greater proportion of variance in wheezing and chest infections during early infancy (2 and 6 months).

3.2. Outcome-wide urban exposome associations in the main analysis

The sparse model selected 13 of the 44 factors (30 %) as non-zero predictors. Notably nine of these predictors showed nonzero coefficients at three or four time points in both outcomes, indicating consistent multi-timepoint associations, while the other four were associated with fewer time points (Figs. 1 and 2, see detailed results in Table S3 and S4). Maternal university education was associated with a decrease in the odds of wheezing and chest infections at 2 months (OR: 0.62, 95 % confidence intervals (CIs): 0.44, 0.91 and OR:0.70, 95 %CI: 0.54, 0.92), as well as time points 6, 12, and 18 months (OR 0.71–0.84; all $p < 0.001$), compared to maternal primary education. Associations in the same direction were also observed for maternal secondary education

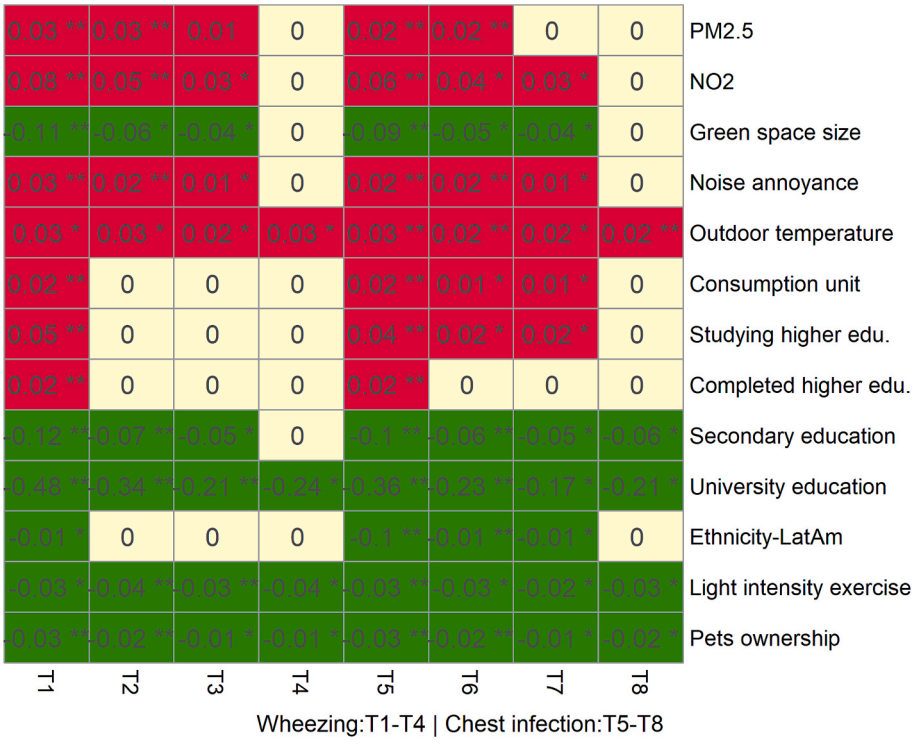

Fig. 1. Heatmap of estimated coefficients for exposure-outcome associations in the mixed-response sparse reduced rank regression (MsRRR) model in the main analysis. Positive (red) and negative (green) coefficients indicate exposures associated with increased and decreased risk, respectively. Cells with "0" indicate no selected association by LASSO penalty. All analyses are adjusted for maternal age, pregnancy BMI, parity, asthma status, COVID-19 pandemic period, and child's sex. * = p value ≤ 0.05, ** = p value ≤ 0.001.

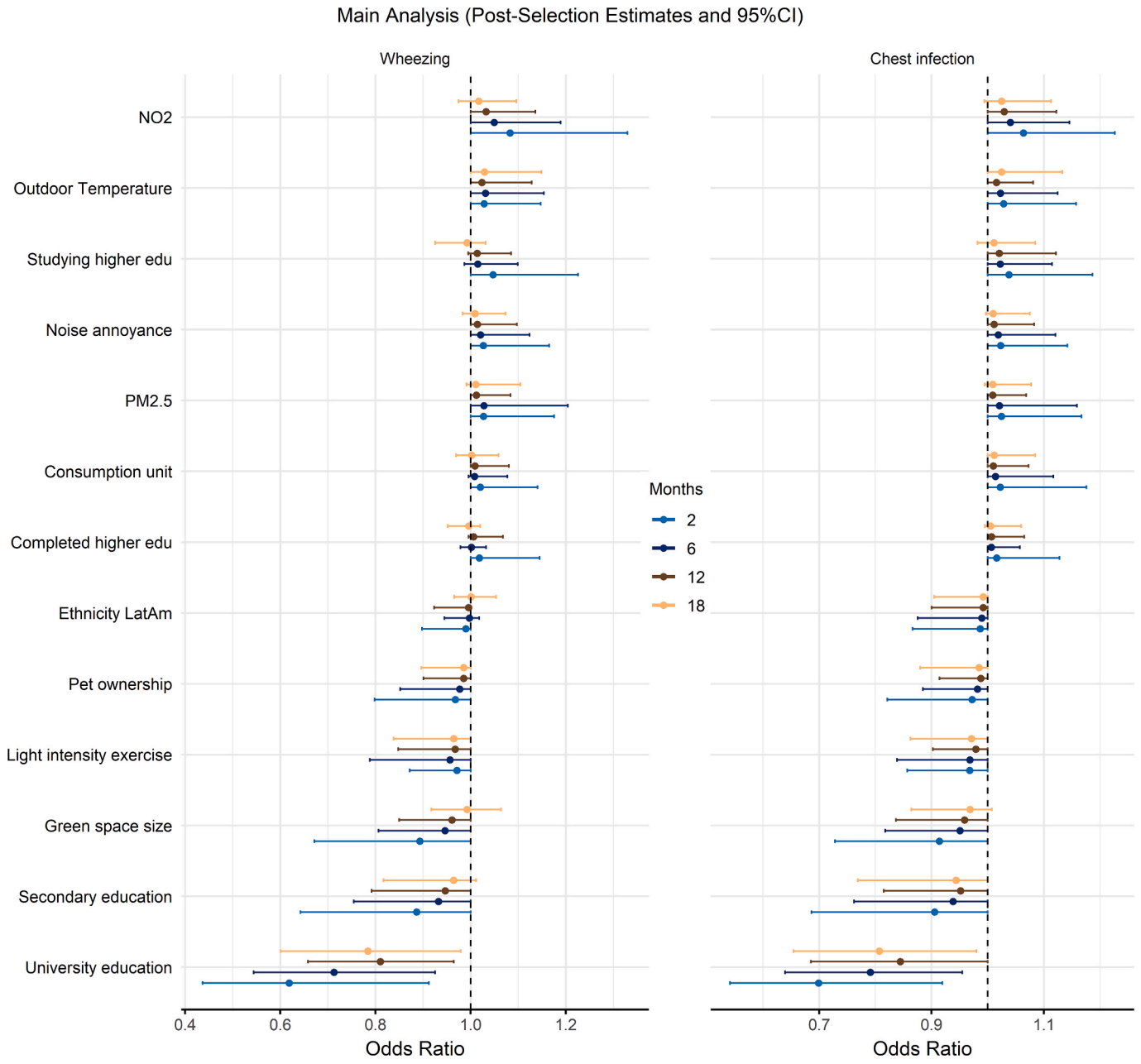

Fig. 2. Post selection odds ratios (OR) and respective 95% confidence intervals (CI) for the selected predictor-outcome associations. Because ORs are reported after LASSO shrinkage, the CI tails can be asymmetric, reflecting the penalized estimation and post-selection inference. Associations were adjusted for maternal age, pregnancy BMI, parity, asthma status, COVID-19 pandemic period, and child's sex.

with both outcomes (OR 0.88–0.94). Higher light-intensity exercise consistently showed associations with a decrease in the outcome odds, with ORs ranging from 0.96 to 0.97 for wheezing and 0.97 to 0.98 for chest infections (all $p < 0.05$). Green space size and pet ownership showed associations in the same direction, though the magnitude varied and the coefficients for some time points were shrunk to zero.

Outdoor temperature was associated with higher odds of wheezing and chest infections at all time-points (OR 1.02–1.03 per 1-SD; all $p < 0.05$). NO_2 (OR 1.02–1.08 per 1-SD; all $p < 0.05$) was consistently associated with higher outcome odds at time points 2, 6, and 12 months. Other detrimental factors were $PM_{2.5}$ (OR 1.01–1.03; all $p < 0.05$) and noise annoyance (OR 1.01–1.03; all $p < 0.05$). Area-level socio-economic indicators, including average income per consumption unit, the proportion of individuals pursuing higher education, and those who have completed higher education, were associated with increased odds of wheezing (2 months) and chest infection (2, 6, and 12 months).

3.3. Stratified analysis

In the sex-stratified analysis, we observed that 17 determinants were selected for females, while 13 determinants were identified in males (Fig. 3 and S8). Association estimates differed by infant sex, with females generally showing stronger associations than males. For instance, BC, surrounding greenspace (i.e. NDVI 50 m), and size of major green space were only selected for females, while maternal Latin American ethnicity was identified only in males. Factors such as NO_2, outdoor temperature, maternal university and secondary education, and time spent in green spaces and light intensity exercise were observed in both sexes.

Results of the sensitivity analysis showed similar exposure-outcome

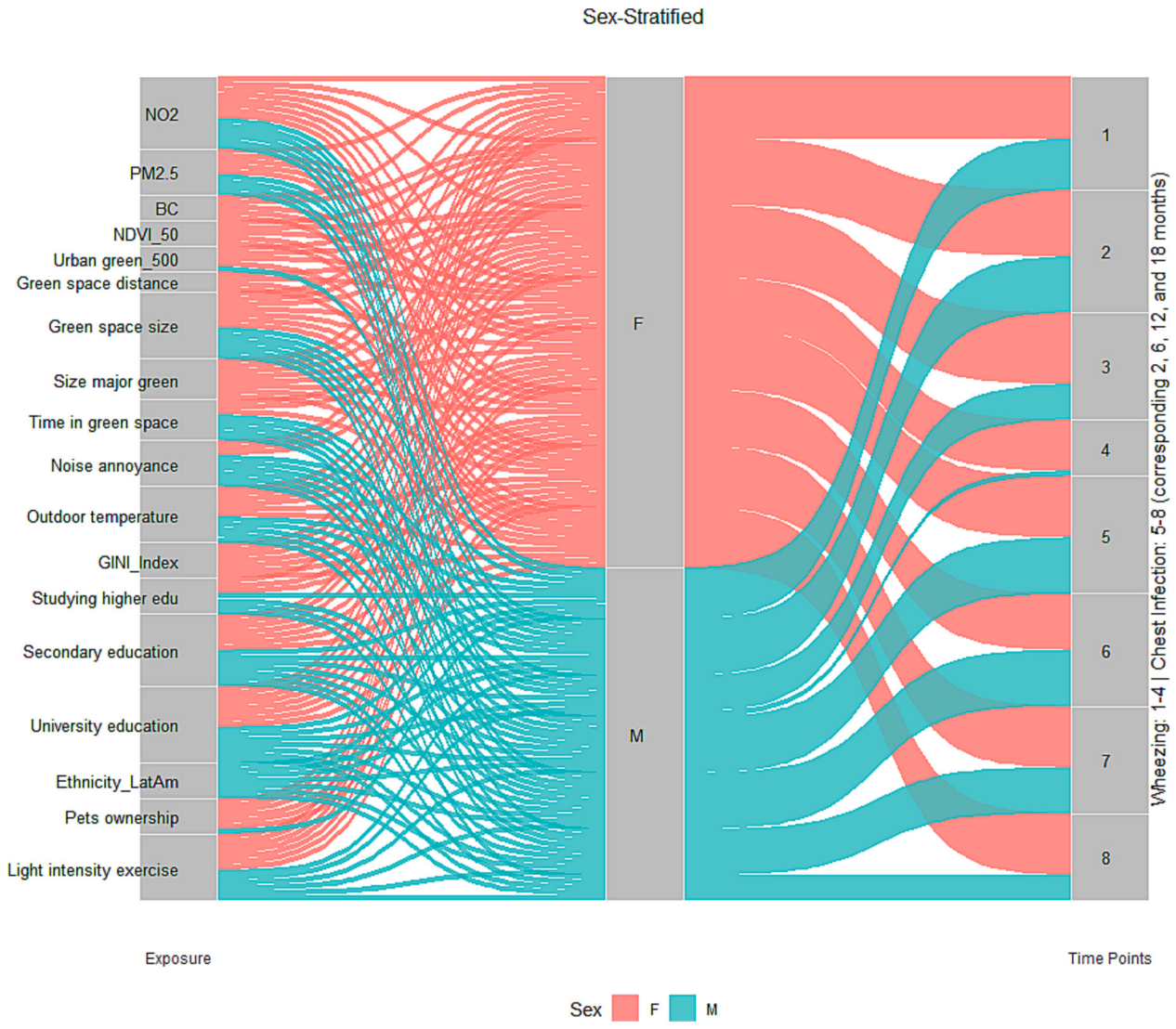

Fig. 3. Sex stratified alluvial plot of exposure-outcome associations in the mixed-response sparse reduced rank regression (MsRRR) model in the main analysis. Flows originate at the left from 18 exposures, pass through the sex strata (Female in red, Male in teal) and terminate at the right on the four time points for each outcome (Wheezing: 1–4, Chest infection: 5–8). Grey ribbon width corresponds to the strength of estimated associations (thicker ribbons = stronger associations). All analyses adjusted for maternal age, pregnancy BMI, parity, asthma status, and COVID-19 pandemic period.

association. Some associations emerged uniquely for wheezing such as alcohol consumption and smoking cessation, associated with increased and decreased risk, respectively (Fig. S6 and S7).

4. Discussion

To our knowledge, this is the first longitudinal study to comprehensively assess the impact of pregnancy urban exposome on infant wheezing and chest infection using an outcome-wide approach. In the main analysis, maternal education, exposure to green spaces, physical activity, pet ownership, and maternal Latin American ethnicity were consistently associated with a decreased risk of both wheezing and chest infection across three or more time points. In contrast, NO_2, $PM_{2.5}$, noise annoyance, outdoor temperature, average income per consumption unit, and the proportion of individuals with ongoing or completed higher education at the census-tract level were associated with an increased risk of both outcomes. For most selected predictors, the largest effect estimates were observed in earlier time points (2–12 months) and attenuated towards the null by 18 months. Overall, these associations suggest a strong early-life exposure–response pattern, likely driven by prenatal influences on fetal lung and immune development. As the immune system matures and postnatal behaviours evolve, susceptibility to environmental insults may decline. Consequently, the apparent attenuation at 18 months may reflect both biological adaptation and reduced precision.

4.1. Air pollution, temperature and noise

Exposure to air pollution, particularly NO_2 and $PM_{2.5}$, during pregnancy is well documented as a critical window of susceptibility for the developing foetus, and has been associated with an increased risk of adverse respiratory outcomes such as wheezing and respiratory infections in childhood (Bettiol et al., 2021; MacIntyre et al., 2014). Our findings are consistent with previous studies that have shown the association of pregnancy exposure to NO_2 and $PM_{2.5}$ with a higher risk of wheezing and respiratory infections in offspring, despite variations in the magnitude of the estimates, particularly for $PM_{2.5}$ (Hua et al., 2023; Hu et al., 2024; Aguilera et al., 2013). However, differences in how exposure levels are quantified may contribute to these discrepancies across studies. Our estimates are expressed per 1-SD increase in exposure, whereas prior studies often report associations using other exposure scales, which may partly explain the variability in the size of the

associations (Bettiol et al., 2021; Madsen et al., 2017). Several biological mechanisms for air pollution have been suggested including oxidative stress and inflammation, placental dysfunction and hypoxia, epigenetics changes, and direct toxic effects on fetal lung development (Saenen et al., 2019). Indirectly, air pollution is also associated with adverse birth outcomes, such as low birthweight, which, in turn increases the risk or susceptibility to respiratory diseases (Sinsamala et al., 2024).

Similar to previous studies (Zheng et al., 2021; Zhang et al., 2023), we found that maternal exposure to higher outdoor temperature during pregnancy was associated with a higher risk of the outcomes, while indoor temperature and humidity were not associated. This may be due to exposure misclassification, given that data on indoor temperature were only available for a two-week period in the entire pregnancy. Evidence on the impact of indoor temperature and humidity during pregnancy on wheezing and chest infection is limited, highlighting the need for further research. High outdoor temperature may disrupt thermoregulation in pregnancy, leading to increased oxidative stress and inflammatory cytokines and reduced blood flow to the placenta (Rook, 2013). Such modifications may influence foetal lung development. Moreover, higher ambient temperature may contribute to heat-induced methylation, particularly in immune and lung development genes, increasing the risk of developing respiratory diseases in the offspring (Fernandes and Lim, 2024).

Noise annoyance was consistently associated with increased risk of wheezing and chest infection. Previous studies have reported associations of noise annoyance with cardiovascular and mental health outcomes, but the relationship between pregnancy exposure and respiratory outcomes in the offspring has rarely been investigated (Recio et al., 2016; Chen et al., 2023). Nevertheless, the few studies that have assessed the association of prenatal noise exposure with preschool wheezing and lung function in childhood (mean age 9.79 years) reported null associations (Abellan et al., 2024). The suggested pathway for noise as a physiological and psychological stressor is through promoting stress response (hypothalamic–pituitary–adrenal, HPA), leading to release of cortisol and other stress hormones (Recio et al., 2016). Additionally, sleep disruption due to noise-related stress may alter the immune system, thereby increasing systematic inflammation in the respiratory system (Recio et al., 2016; Abellan et al., 2024).

4.2. Natural spaces

In the present study, we observed that the most consistent protective association identified was the size of green space (<5000 m^2) near maternal residence during pregnancy (Dadvand et al., 2024). This likely reflects enhanced accessibility and frequent use of nearby green space, consistent with evidence that small 'pocket' parks increase local accessibility and use (Cohen et al., 2014; Kaczynski et al., 2014). However existing literature on associations between greenness exposure and respiratory health is inconsistent, showing protective, harmful or null associations (Johannessen et al., 2023; Wu et al., 2022; Mueller et al., 2022). The biological mechanisms underlying the protective associations of green spaces involve both direct and indirect pathways. Green spaces are known to reduce psychological stress and thereby lowering cortisol levels and reducing inflammatory markers (Jimenez et al., 2021). Low stress levels could also improve placental function, ensuring better transfer of oxygen and nutrients to the foetus and hence promoting healthier pregnancy and long-term well-being for the child (Kramer et al., 2023) Furthermore, access to green spaces might encourage physical activity and provide opportunities for social contact and community engagement (Gascon et al., 2017). Moreover, natural environments promote exposure to diverse microbial components, which, in turn, enhances maternal-offspring immune function and development (Rook, 2013; Fernandes and Lim, 2024). Other beneficial mechanisms include air pollution and noise reduction and thermoregulation through the cooling effect (Johannessen et al., 2023; Markevych et al., 2017). However, green spaces can also pose health risks, such as increased exposure to pollen, which can generate pollen sensitization and trigger allergies and asthma, and also exposure to other allergens, such as fungal spores and outdoor mold, that may negatively impact respiratory health in the offspring (Johannessen et al., 2023).

4.3. Social exposome

Among social exposome factors, we observed a consistent and strong association of maternal university and secondary education levels with lower risk of wheezing and chest infection at all follow-ups. Maternal education level is a known social determinant of health, which may also influence offspring health through various social and biological pathways (Choudhary et al., 2024). Additionally, the risk of wheezing and chest infection was decreased in the offspring of Latin American mothers in comparison with the offspring of European mothers, specifically within the 12-month period. However, interpreting these results is challenging due to inconsistent evidence (Camacho-Rivera et al., 2015; Gabriele et al., 2012). In contrast to the findings for individual-level SES indicators, we observed that a higher average income and a greater proportion of individuals with higher education at the census-tract level were associated with an increased risk of both outcomes, though associations were more consistent with chest infection at 2, 6, and 12 months. This highlights the complex and multifaceted relationship between SES and health. SES is a multidimensional construct encompassing various independent but correlated indicators, such as income, education, occupation, and neighbourhood characteristics, which may influence health through different pathways (Robinson et al., 2018; Oakes and Rossi, 2003). The findings on neighbourhood-level SES should be interpreted cautiously as they may reflect contextual confounding rather than a protective association of lower neighbourhood-level SES. In Barcelona, higher SES neighborhoods tend to have higher levels of air pollution and noise, which could partly explain our observed association of neighborhood-level SES and respiratory outcomes (Martori et al., 2022).

The mechanisms through which the social exposome operates during pregnancy include behavioural, material and psychosocial factors that influence the social-to-biological processes (Gudi-Mindermann et al., 2023). Social exposome factors related to maternal harmful behaviours, such as smoking and alcohol consumption, and poor diet may have profound long-term biological impact on foetal development (Albers et al., 2018; Gluckman et al., 2008). For instance, smoking prevalence is higher among individuals with lower education attainment, contributing to adverse birth and early-life health outcomes (Cao et al., 2023). Additionally, material factors related to physical and chemical exposures, and psychosocial stressors (e.g., job strain and discrimination) during sensitive developmental windows can trigger biological processes that may disrupt normal fetal development (Entringer et al., 2015; Vrijheid et al., 2016). Poor maternal diet including inadequate nutrition or excessive consumption of unhealthy processed food during pregnancy may impair fetal immune and lung development (Mayor et al., 2015). These pathways may act simultaneously and interactively, influencing both short and long-term respiratory outcomes in children (Neufcourt et al., 2022).

4.4. Lifestyle factors

In the present study many lifestyle-related determinants were covered compared to other previous epidemiological studies. Among the lifestyle factors, performing light intensity activities and pet ownership during pregnancy were associated a lower risk across all the outcome domains. The findings on light intensity activities are consistent with previous studies that have reported protective associations of physical activity during pregnancy with respiratory outcomes of the offspring. Exercise during pregnancy is associated with several benefits for the mother and the foetus through various biological processes, including the formation of new blood vessels in the placenta, increased resistance

to oxidative stress and lipid peroxidation and lower vasoconstrictor levels (endothelin-1), thereby improving fetoplacental blood flow (Rodríguez and González, 2014).

Generally, findings from previous studies on the relationship between pet ownership and respiratory outcomes have been inconsistent. The discrepancies in the findings have been attributed to pet-specific differences, including variations in allergen and microbial diversity, which warrant further investigation. The mechanisms of pet ownership and potential beneficial associations could be interpreted based on the hygiene hypothesis. Exposure to pets in early life may expose to a variety of microbes and allergens that stimulate the innate immune system, shifting the immune response from a Th2 profile, which promotes allergy, to a Th1 profile, which is associated with reduced Immunoglobulin E production and lower risk of atopy (Aichbhaumik et al., 2008).

4.5. Strengths and limitations

The main strengths of this study include its prospective cohort design involving mother–child pairs, which allowed for a comprehensive assessment of different aspects of exposures and lifestyle factors during pregnancy through a combination of personal monitoring, modelling and questionnaires to characterise the urban exposome. Additionally, the BiSC cohort characterized participants' time activity pattern to assess the exposome across home, workplace, and commuting route, an approach rarely undertaken in previous studies (Dadvand et al., 2024). This is the first longitudinal study to examine pregnancy urban exposome in relation to multiple time-points for infant respiratory outcomes using the outcome-wide exposome approach. This approach offers several methodological advantages, including accounting for correlated factors and outcomes, identifying weak and ambiguous associations, controlling for multiple testing, and handling incomplete records (VanderWeele et al., 2020; Luo et al., 2018; Kundu et al., 2020). By borrowing strength across exposure-outcome pairs with similar association patterns, this approach boosts the power to detect true signals that might otherwise be missed by traditional single-outcome methods (Anguita-Ruiz et al., 2023; Kundu et al., 2020).

Despite these strengths, the study had some limitations. Although we incorporated the group-lasso penalization, which shrinks less important coefficients to zero, along with stability selection techniques, such as bootstrapping (Anguita-Ruiz et al., 2023), we acknowledge that promoting sparsity may reduce variance, but may also introduce bias if important variables are shrunk, reflecting the bias-variance trade-off (Tibshirani, 1996) Despite that the model accounts for dependencies across outcomes, it does not explicitly handle temporal autocorrelation. As a result, the model does not infer any temporal trend of the outcomes. Attrition is another challenge as there was a 10.2 % loss to follow-up between baseline and the 18-month assessment, which could introduce non-random bias and limit generalizability (Dadvand et al., 2024) Single imputation analysis can bias estimates if the imputed dataset differs from the expected mean of multiple imputations, however, the stability-selection and bootstrapping procedures might have partially compensated for the underestimation of variance. In addition, maternal self-reporting of offspring health information may be subject to reporting bias. However, the use of the validated ISAAC questionnaire, along with frequent follow-ups and data collection at multiple postnatal time points, helped mitigate some degree of bias. Despite the use of innovative methodologies for exposure assessment, measurement error is unavoidable to varying degrees across different environmental factors. Dichotomization of occasional and recurrent wheezing may obscure potential dose–response relationships. We acknowledge that the set of 44 factors does not capture all possible pregnancy exposures. Additionally, we did not consider postnatal factors such as air pollution, which were likely similar to pregnancy exposure based on residential address, assuming no change in residence. Finally, as with other observational studies, unmeasured confounding may still bias the results, even after controlling for covariates associated with both predictors and outcomes.

4.6. Conclusion

This outcome-wide exposome study strengthens evidence linking exposure to urban environments during pregnancy with infant respiratory outcomes. It highlights how noxious environmental exposures and access to green spaces during pregnancy, as well as maternal risk factors can jointly influence offspring respiratory outcomes in early life. Furthermore, by identifying important environmental determinants that simultaneously influence respiratory health outcomes at different time points, this study provides valuable insights that could inform the prioritization of the most relevant factors and developing more effective and targeted public health interventions and policy measures, ultimately leading to a greater impact on population health.

CRediT authorship contribution statement

Robin M. Sinsamala: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Augusto Anguita-Ruiz:** Writing – review & editing, Methodology, Formal analysis. **Xavier Basagaña:** Writing – review & editing, Resources, Methodology, Conceptualization. **Maria Foraster:** Writing – review & editing, Data curation. **Mireia Gascon:** Writing – review & editing, Resources, Conceptualization. **Elisa Llurba:** Writing – review & editing, Resources, Conceptualization. **Chongliang Luo:** Writing – review & editing, Methodology. **Mark J. Nieuwenhuijsen:** Software, Methodology, Conceptualization. **Cecília Persavento:** Resources, Project administration, Investigation. **Ioar Rivas:** Writing – review & editing, Investigation, Conceptualization. **Yu Zhao:** Writing – review & editing, Validation. **María Dolores Gómez-Roig:** Writing – review & editing, Resources, Investigation, Conceptualization. **Jordi Sunyer:** Resources, Funding acquisition, Conceptualization. **Alessandro Marcon:** Writing – review & editing, Validation, Supervision. **Ane Johannessen:** Writing – review & editing, Validation, Supervision, Funding acquisition. **Payam Dadvand:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109900.

Data availability

Data will be made available on request.

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