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Exposure to outdoor residential noise during pregnancy, embryonic size, fetal growth, and birth outcomes

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ABSTRACT

Introduction: Previous literature suggested that noise exposure during pregnancy was not associated with adverse birth outcomes. However, no studies evaluated the association between noise exposure and embryonic and fetal growth, or mutually assessed other urban environmental exposures such as traffic-related air pollution or natural spaces.

Methods: We included 7947 pregnant women from the Generation R Study, the Netherlands. We estimated total (road traffic, aircraft, railway, and industry), road traffic, and railway noise at the participants' home addresses during pregnancy using environmental noise maps. We estimated traffic-related air pollution using land-use regression models, greenness within a 300 m buffer using the normalized difference vegetation index, and distance to blue spaces using topographical maps at the home addresses. Embryonic size (crown-rump length) and fetal growth parameters (head circumference, femur length, and estimated fetal weight) were measured by ultrasound at several gestational ages. Information on neonatal anthropometrics at birth (head circumference, length, and weight) and adverse birth outcomes (preterm birth, low birth weight, and small for gestational age) were retrieved from medical records.

Results: Higher total noise exposure during pregnancy was associated with larger crown-rump length (0.07 SDS [95%CI 0.00 to 0.14]). No association was found with fetal growth parameters, neonatal anthropometrics, and adverse birth outcomes. Similar results were observed for road traffic noise exposure, while railway noise exposure was not associated with any of the outcomes. Traffic-related air pollution was not associated with crown-rump length. Total noise exposure mediated 15% of the association between exposure to greenness and smaller crown-rump length. No association was observed between distance to blue spaces and total noise exposure.

Conclusion: Exposure to outdoor residential noise during pregnancy was associated with larger embryonic size. Moreover, a reduction of total noise exposure during pregnancy partially mediated the association between exposure to greenness and smaller embryonic size. Additional research is warranted to confirm and further understand these novel findings.

1. Introduction

Noise is considered one of the most common environmental risk factors to health and wellbeing.(Khomenko et al., 2022; World Health Organization, 2018) The most prevalent source of environmental noise in Europe is road traffic, followed by railway, aircraft and industry. (European Environment Agency, 2017b) Motorized traffic not only leads to exposure to noise but also to air pollution. Worldwide, an increasing number of people is exposed to adverse urban environments, including higher noise levels, poorer air quality, and less access to natural spaces

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including greenness and blue spaces.(United Nations, 2019).

Apart from auditory effects, noise exposure has also been associated with both physiological and psychological health, including cardiovascular and metabolic disorders and sleep disturbances.(van Kamp et al., 2020; Van Kempen et al., 2018) Several studies have investigated the association between environmental noise exposure during pregnancy, mainly from aircraft and road traffic sources, and birth outcomes including birth weight, preterm birth, and being born small for gestational age.(Clark et al., 2020; Dzhambov and Lercher, 2019; Nieuwenhuijsen et al., 2019; Nieuwenhuijsen et al., 2017b; Smith et al., 2020) Findings are inconsistent across studies, but three systematic reviews concluded that there was no evidence of an association between road traffic noise exposure and birth outcomes based on an overall moderate to high quality of evidence of the included studies.(Clark et al., 2020; Dzhambov and Lercher, 2019; Nieuwenhuijsen et al., 2017b) Moreover, they concluded that there was an association between aircraft and railway noise exposure and birth outcomes based on a very low overall quality of evidence of the included studies. (Clark et al., 2020; Nieuwenhuijsen et al., 2017b) Additionally, traffic-related air pollution exposure during pregnancy, an important co-exposure of road traffic noise exposure, has been related to adverse birth outcomes.(Boogaard et al., 2022) Exposure to greenness during pregnancy has been associated with larger fetal size and better birth outcomes (Akaraci et al., 2020; Hu et al., 2021; Lin et al., 2020; Torres Toda et al., 2022), while the results of the association between exposure to blue spaces and birth outcomes were mixed.(Akaraci et al., 2020; Hu et al., 2021).

Importantly, no previous studies have explored the association of environmental noise exposure during pregnancy with embryonic size and fetal growth parameters. Altered embryonic and fetal growth rates are markers of the fetal response to an adverse intra- and extra-uterine environment.(Gluckman et al., 2008; Mook-Kanamori et al., 2010) These adaptations result in changes in tissue and organ development and are not necessarily visible at birth.(Fleming et al., 2018; Gluckman et al., 2008) Moreover, embryonic and fetal growth and development are determinants for health and disease in later life, according to the Developmental Origins of Health and Disease paradigm.(Barker, 2007; Gluckman et al., 2008; Mook-Kanamori et al., 2010; Steegers-Theunissen et al., 2009) Also, previous studies did not consistently investigate the role of traffic-related air pollution as a co-exposure or as effect modifier on the association between noise exposure and birth outcomes, as well as the mediating role of noise exposure on the association between natural spaces and birth outcomes.(Dzhambov et al., 2018; Markevych et al., 2017).

Therefore, we first examined the association between exposure to outdoor residential total noise (i.e., road traffic, railway, aircraft and industry), road traffic noise, and railway noise exposure during pregnancy and embryonic size and fetal growth parameters and birth outcomes in a large population-based prospective cohort study. Second, we investigated whether an association between noise exposure and a specific outcome identified in the first aim was confounded by traffic-related air pollution exposure or whether traffic-related air pollution exposure modified the observed association. Third, we assessed whether noise exposure mediated a possible association between exposure to greenness or distance to blue spaces and any of the outcomes mentioned above.

2. Methods

2.1. Population and study design

This study was embedded in the Generation R Study, a prospective population-based cohort from early in pregnancy onwards in the city of Rotterdam, the Netherlands.(Kooijman et al., 2016) The study design and participant sampling has been described in detail previously.(Jaddoe et al., 2006) In brief, mothers were eligible for the cohort if they had an expected delivery date from April 2002 until January 2006 and were living in the study area. In total, 8879 mothers were enrolled in the full Generation R study during pregnancy. For the present study, we included a total of 7947 women (Fig. 1). We excluded twin pregnancies, terminated pregnancies and intra-uterine deaths. Moreover, pregnancies without any data on noise exposure during pregnancy and with no measurements of embryonic size, fetal growth or birth outcomes were excluded. The study protocol was approved by the Medical Ethical Committee of Erasmus Medical Centre, Rotterdam (MEC 198.782/2001/31). Written informed consent was obtained from all participants.

2.2. Outdoor residential noise exposure

Source-specific environmental noise maps from 2012 developed by the DCMR Rijnmond Environmental Service for Rotterdam area were used. Noise maps included information from road traffic, aircraft, railway, industry, and total noise to estimate annual average levels of outdoor residential noise exposure. These maps met the requirements of the European Environmental Noise Directive, and were based on buildings covering the residential areas of Rotterdam, Maassluis, Rozenburg, Schiedam, and Vlaardingen.(European European Union, 2002) A standard method named 'Standaard Rekenmethoden' (SRM) was used which included surfaces polygon, buildings, barriers, slope, crossings, roundabouts as well as the corresponding emission sources for each of the specific models. Briefly, the noise level at the geocoded point was determined by the noise emission of the source and other terms that denoted the attenuation from source to receiver due to geometric spreading, air absorption, ground impedance, noise barriers as well as wind directions and temperature gradients. Noise levels were estimated at a height of 4 m at the most exposed façade of the residential addresses. An intersect was done from the buildings noise data with the geocodes. In case the geocode was outside the building, but in less than 50 m, it was assigned to the closest building (3.8% of the addresses). For each noise source, the day-evening-night noise indicator (L_{DEN}) was calculated as the A-weighted average sound level over the entire 24-hour day with penalties for the evening (+5 decibel (dB); 4 h, 19:00–23:00) and the night (+10 dB, 8 h, 23:00–07:00).(Gan et al., 2012) The specific equations used for the noise estimations of each noise source and the total noise exposure are described in **Methods S1.**

The levels of L_{DEN} of each noise exposure source and of the total noise exposure were applied to each geocoded participant's address reported for the pregnancy period. When a participant reported more than one address, average noise levels over the entire pregnancy were calculated by weighting the noise levels estimated at each address based on the time spent living at each address. We assumed that noise exposure levels remained relatively stable during the studied period, as the European Environment Agency recently indicated for the period between 2007 and 2012.(European Environment Agency, 2017a) For our analyses we took into account total noise, road traffic, and railway noise exposure. A smaller proportion of women in our population were exposed to the other noise sources with levels above 40 dB (i.e., aircraft, and industry), considering the minimum reliable value (11.6%, and 21.5% respectively) and therefore we did not assess them separately.

2.3. Traffic-related air pollution exposure

The concentrations of nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) during pregnancy (i.e., from conception until birth) were estimated using land-use regression models.(Beelen et al., 2013; Eeftens et al., 2012) Between February 2009 and February 2010, NO_2 was measured in 80 sites spread throughout the Netherlands and Belgium and $PM_{2.5}$ in 40 of these sites. An annual mean concentration for each pollutant was calculated averaging the results of all measurements, while using data from a continuous reference site to adjust for temporal trends. Next, land-use regression models were developed, and air pollution levels were estimated at each geocoded participant's address reported for the

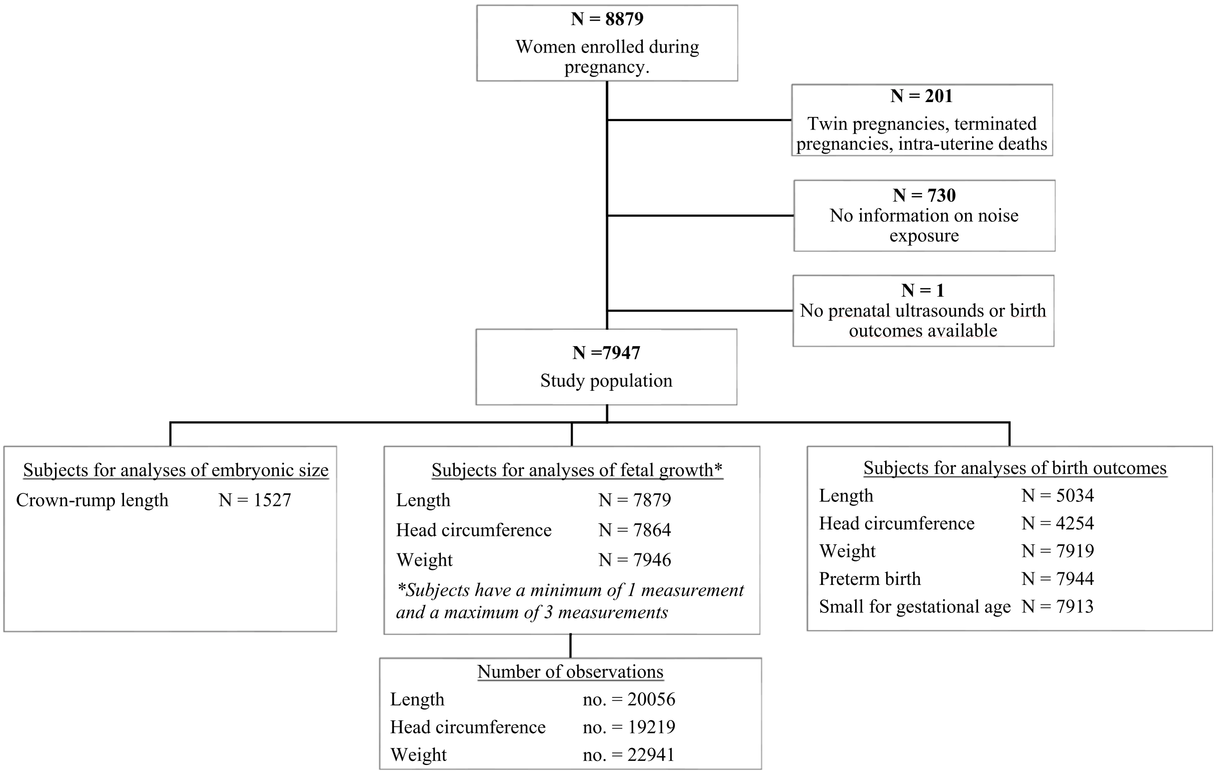


Fig. 1. Flowchart of the study population.

pregnancy period. When a participant reported more than one address, average air pollution levels over the entire pregnancy were calculated by weighting the air pollution levels estimated at each address based on the time spent living at each address.

2.4. Natural spaces exposure

Exposure to residential surrounding greenness around each maternal place of residence was estimated using a satellite image–based vegetation index, the Normalized Difference Vegetation Index (NDVI).(Nieuwenhuijsen et al., 2014) The NDVI was derived from the Landsat 4–5 Thematic Mapper (TM), Landsat 7 Enhanced Thematic Mapper Plus (ETM +), and Landsat 8 Operational Land Imager (OLI) /Thermal Infrared Sensor (TIRS) with 30 m × 30 m resolution to determine the level of exposure to surrounding green spaces.(Herring and Weier, 2000) NDVI quantifies greenness by measuring the difference between near-infrared (which vegetation strongly reflects) and red light (which vegetation absorbs). NDVI values range from 0 to 1, with higher numbers indicating more greenness. To achieve maximum exposure contrast, we used available cloud-free Landsat images during the period between May and August for the years relevant to our period of study and calculated greenness within 300 m buffers around each address.

Distance to major blue spaces (sea, lake, fish ponds, rivers, canals) was calculated from topographical maps or local sources as the straight-line distance from the home to nearest blue space with an area greater than 5000 m^2 (Nieuwenhuijsen et al., 2014).

To obtain the final mean exposure to residential greenness and distance to blue spaces during pregnancy, we weighted the exposure based on the time spent at each home address for all participants.

2.5. Embryonic size and fetal growth parameters and birth outcomes

Ultrasound examinations were carried out by experienced sonographers during visits to one of the research centers and took place at early, mid-, and late pregnancy. At early pregnancy visits (<14 weeks), crown-rump length was measured as a parameter of embryonic size. At the mid-pregnancy (20 weeks) and late pregnancy (30 weeks) visits, femur length and head circumference were measured as fetal growth parameters. Estimated fetal weight was calculated using the Hadlock formula.(Hadlock et al., 1985) The methods of ultrasound examinations are described in detail in **Methods S2**.

From midwifery registries and obstetric medical records, we obtained neonatal anthropometrics at birth (length, head circumference, and weight). For each ultrasound measurement, standard deviation scores (SDS) were then constructed based on reference growth curves from the whole study population, adjusted for gestational age at the time of the measurement.(Verburg et al., 2008) For each birth measurement, SDS were constructed using growth standards adjusted for gestational age at the time of birth and sex of the baby.(Niklasson et al., 1991).

Low birth weight was defined as birth weight < 2500 g. Low birth weight at term was defined as birth weight < 2500 g neonates born after 37 weeks of gestation. Small size for gestational age at birth was defined as a sex and gestational age adjusted birth weight below the 10th percentile in the study population. Preterm birth was defined as a gestational age of < 37 weeks at delivery.

2.6. Pregnancy dating and gestational age at each assessment

Precise dating of the pregnancy is key for properly defining the gestational age of each ultrasound and birth measurements. For pregnancy dating of early pregnancy embryonic size measurements, gestational age was based on a known and reliable last menstrual period but only in the cases of a regular menstrual cycle.(Slama et al., 2008) The last menstrual period and additional information on cycle regularity and duration was obtained from the referral letter and through questionnaires and confirmed at enrolment. Women with an irregular menstrual cycle were not included in the embryonic size analysis since gestational age could not be determined.

For pregnancy dating of mid- and late-pregnancy fetal growth measurements and neonatal anthropometrics at birth, gestational age was established by first trimester crown-rump length (gestational age below 12 weeks and five days of gestation, and crown-rump length measurement smaller than 65 mm) or biparietal diameter (gestational age from 12 weeks and five days of gestation onwards, and biparietal diameter>23 mm).

2.7. Covariates

Covariates were selected based on a Directed Acyclic Graph (Figure S1).(Textor et al., 2016; VanderWeele et al., 2008) Information on socioeconomic indicators and lifestyle behaviors was collected by means of questionnaires administered at several times during pregnancy. The following variables were extracted from the questionnaires and created: maternal age at enrollment (years), maternal national origin (Dutch; Moroccan; Turkish; Surinamese / Dutch Antilles; other European; other non-European), educational level (low: no or primary education; medium: secondary education; high: university degree), household income (<€900; €900-€1600; €1600-€2200; >€2200), maternal periconceptional smoking (yes; no), maternal alcohol consumption during pregnancy (never in pregnancy; until pregnancy was known; continued in pregnancy occasionally; continued in pregnancy frequently), maternal periconceptional folic acid use (yes; no), and maternal parity (nulliparous; one; two or more).

Child sex was obtained from midwifery registries and obstetric medical records. Neighbourhood socioeconomic status (SES) score at each maternal residential address was determined by the average monthly household income, the number of non-employed residents, the number of lower educated residents, and the number of households with a low income (National Institute for Public Health and the Environment, 2017). A higher neighbourhood SES score represents a more affluent neighbourhood.

2.8. Statistical analyses

2.8.1. Missing data

The percentage of missing values of covariates was lower than 20%, except for information on monthly household income and folic acid use during pregnancy (22.9% and 25.5%, respectively). Missing data of the covariates were imputed using the Markov chain Monte Carlo approach for multiple imputations to limit selection bias and loss of statistical power. A total of 25 complete datasets were obtained and analyzed using standard procedures for multiple imputation (i.e., Rubin's rules). (Graham et al., 2007; Sterne et al., 2009) Distributions in the imputed and observed datasets were comparable (Table S1).

2.8.2. Non-response analysis

Pregnant women included in the analyses were more likely to have a Dutch national origin, a higher education, a higher monthly household income, continued drinking alcohol occasionally during pregnancy and taken periconceptional folic acid compared to the women not included (Table S2). Inverse probability weighting was performed for all analysis to account for selection bias, by using information available from the population included during pregnancy (N = 8678) to predict the probability of participation in the present study. The inverse of those probabilities was used as weights in the analyses to ensure representative results for the initial population of the cohort and were used in all subsequent analyses.(Weisskopf et al., 2015; Weuve et al., 2012) The variables used to create the weights in each analysis can be found in Table S3.

2.8.3. Noise exposure association analysis

Linear regression analyses were performed to assess the association between total noise exposure during pregnancy and early pregnancy embryonic size (i.e., crown-rump length). To assess the association between total noise exposure during pregnancy and repeatedly measured fetal growth across pregnancy, we used unbalanced repeated measurement regression models. SDS of fetal growth parameters in mid-pregnancy and late pregnancy (i.e., femur length, head circumference, and estimated fetal weight), and at birth (i.e., length, head circumference, and birth weight) were used. These models take into account the correlation between the repeated measurements of the same subject, and allow for incomplete outcome data.(Goldstein, 2011) Linear regression analyses were performed to assess the association between total noise exposure during pregnancy and neonatal anthropometrics at birth (i.e., length, head circumference, and weight). Logistic regression analyses were used to assess the association between total noise exposure during pregnancy and adverse birth outcomes (i.e., low birth weight (at term), preterm birth, and SGA).

We first ran all models unadjusted, second we ran minimally adjusted models, adjusting for the covariates that are antecedent to noise exposure and the outcomes (i.e. maternal age at enrollment, maternal national origin, maternal educational level, monthly household income, residential greenness, and neighbourhood SES score), and lastly we ran fully adjusted models additionally adjusting for lifestyle factors, parity, and fetal sex. The assumptions of the linear regression models, including linearity between each exposure and each outcome, normality of the residuals, homoscedasticity, and no collinearity between covariates, were fulfilled.

As a sensitivity analysis, we repeated all analyses investigating the association between solely road traffic noise exposure and railway noise exposure with each outcome. Also, we performed linear regression analysis to assess the association between total noise exposure during pregnancy and fetal growth parameters in mid- and late pregnancy. For these analyses, the assumptions of the linear regression models were also fulfilled. We additionally explored the potential effect modification by maternal age, maternal national origin (Dutch *vs* non-Dutch), maternal educational level and season of birth, by adding a product interaction between noise exposure and each of these variables separately. We quantified the potential differences by performing stratified analysis.

2.8.4. Traffic-related air pollution as co-exposure or as effect modifier

When an association between noise exposure and a specific outcome was identified, we ran a regression model of NO_2 and $PM_{2.5}$, separately, with that specific outcome. If an association of one of these traffic-related air pollutants was observed, we ran regression models mutually adjusting for noise exposure and the air pollutant. Moreover, we explored potential effect modification by NO_2 and $PM_{2.5}$ and quantified the potential differences by performing stratified analysis.

2.8.5. Noise as mediator between natural spaces and the outcomes

When an association between noise exposure and a specific outcome was identified, we ran a regression model of greenness and distance to blue spaces, separately, with noise exposure. If an association of one of these natural spaces indicators was observed with noise exposure, we applied a mediation analysis for estimating whether a part of the association between the natural spaces indicator and the specific outcome was mediated by noise exposure (R package: mediation).(Tingley et al., 2014; Valeri and Vanderweele, 2013) Standard errors were calculated using bootstrapping. We estimated the natural direct effect, the natural indirect effect, and the total effect. We calculated the proportion mediated as the natural indirect effect divided by the total effect.

All statistical analyses were performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of the study population

A total of 7947 pregnant women were included in this study (Fig. 1). Women were on average 29.8 years of age and 49.9% had a Dutch national origin (Table 1). In total, 5.4% of the children was born preterm and 9.2% was born small for gestational age. The average gestational

Table 1
Maternal and child characteristics of the study population (N = 7947).

Characteristics	Distribution
Noise exposure	
Total noise exposure (L_{DEN}) (dB)	55.3 (50.2; 61.5)
Road traffic noise exposure (L_{DEN}) (dB)	54.0 (48.0; 61.0)
Railway noise exposure (L_{DEN}) (dB)	41.0 (40.0; 44.0)
Maternal characteristics	
Maternal age at enrollment (years)	29.8 (±5.3)
Maternal national origin	
Dutch	49.9%
Moroccan	7.1%
Turkish	9.4%
Surinamese/Dutch Antilles	12.3%
Other European	7.6%
Other non-European	13.8%
Maternal educational level	
Low	26.9%
Medium	30.6%
High	42.5%
Monthly household income	
<900 euro	12.0%
900–1600 euro	17.8%
1600–2200 euro	15.1%
>2200 euro	55.1%
Periconceptional smoking (yes *vs.* no)	27.0%
Alcohol consumption during pregnancy	
Never in pregnancy	47.6%
Until pregnancy was known	12.7%
Continued in pregnancy occasionally	32.2%
Continued in pregnancy frequently	7.5%
Periconceptional folic acid use (yes *vs.* no)	40.5%
Parity	
0 children	55.0%
1 child	30.4%
2 or more children	14.6%
NO_2 (μg/m^3)	34.0 (31.9; 36.5)
$PM_{2.5}$ (μg/m^3)	16.8 (16.6; 17.2)
Residential greenness in 300 m buffer	0.37 (±0.1)
Distance to blue spaces (m)	281.8 (135.2; 484.4)
Residential neighbourhood SES score	−1.1 (-2.1; 0.1)
Child characteristics	
Sex (boy *vs.* girl)	50.2%
Gestational age at birth (weeks)	39.9 (37.0; 42.1)
Preterm birth	5.4%
Birth weight (grams)	3420 (±557)
Low birth weight	4.8%
Low birth weight at term	1.9%
Small for gestational age	9.2%

Abbreviations: dB, decibel; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; SES, socioeconomic status; Data are presented as percentage for categorical variables, mean (standard deviation) for continuous variables with a normal distribution, and median (25th; 75th percentile) for continuous variables with a skewed distribution.

age at birth was 39.9 weeks and the average birth weight was 3420 g. Median total noise exposure during pregnancy was 55.3 dB, median road traffic noise exposure was 54.0 dB, and median railway noise exposure was 41.0 dB. Total noise exposure levels were strongly correlated with road traffic noise exposure levels, and moderately correlated with railway noise exposure (0.97 and 0.21, respectively) (Table S4). Total noise exposure was weakly correlated with exposure to greenness and distance to blues spaces (-0.13 and −0.01, respectively), and moderately correlated with traffic-related air pollutants (0.30 for NO_2, and 0.35 for $PM_{2.5}$).

Mothers who were nulliparous, reported periconceptional smoking, lived in a neighbourhood with a lower SES score and less residential greenness around their house had a higher total noise exposure during pregnancy (Table S5). Children of mothers who were older and exposed to less residential greenness had a larger crown-rump length in early pregnancy (Table S5). However, mothers with a higher educational level, higher monthly household income, a Dutch national origin, and who were multiparous, older, did not report periconceptional smoking or folic acid use, and lived in a neighbourhood with a higher SES score and more greenness around their house had children with a larger length at birth and higher birth weight (Table S5).

3.2. Noise exposure, embryonic size, fetal growth parameters, and birth outcomes

In unadjusted models, higher total noise exposure during pregnancy was associated with larger first trimester crown-rump length (0.07 SDS [95% CI 0.00 to 0.14] per 10 dB increase) (Fig. 2, Table S6). Results remained after adjusting for covariates. Total noise exposure during pregnancy was not associated with fetal length, head circumference, or weight during pregnancy (Fig. 2, Table S6-S7). No associations were found between total noise exposure during pregnancy and neonatal anthropometrics at birth (i.e., birth length, birth weight, head circumference at birth, and birth weight), nor with any adverse birth outcomes (i.e., low birth weight (at term), preterm birth and small for gestational age) (Fig. 3A-C, Table S8-S9).

Effect estimates were materially unchanged when assessing the association between road traffic noise exposure during pregnancy and embryonic size, fetal growth and birth outcomes (Table S6, S8-S9). Railway noise exposure was not associated with any of the outcomes (Table S6, S8-S9).

We did not identify an effect modification by maternal age, maternal national origin (Dutch *vs* non-Dutch), maternal educational level and season of birth on the association between total noise exposure and first trimester crown-rump length (p-value for interaction > 0.05). However, stratified analysis showed an association between noise exposure and embryonic growth in women aged $\leq$ 28 years, of non-Dutch national origin, and with a delivery date in spring (Table S10).

3.3. Traffic-related air pollution as co-exposure or as effect modifier

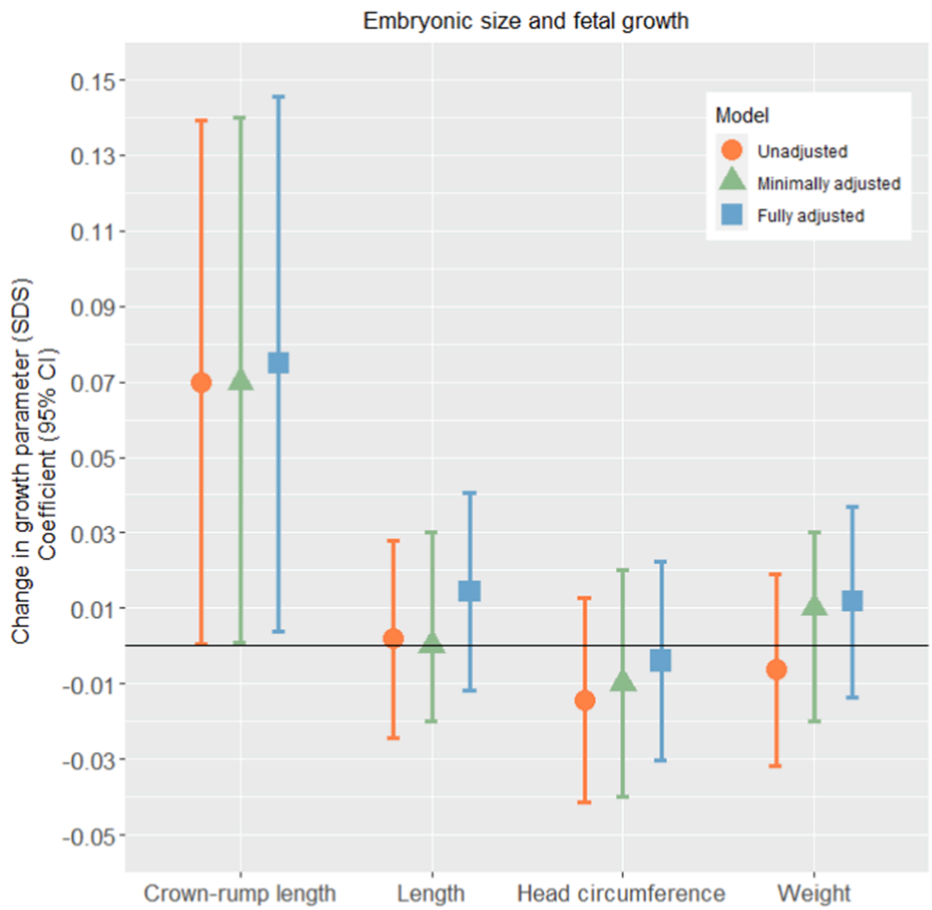
No association was observed between exposure to NO_2 and $PM_{2.5}$ during pregnancy and first trimester crown-rump length (Table S11). Also, we did not identify an effect modification by exposure to traffic-related air pollution (NO_2 and $PM_{2.5}$) on the association between total noise exposure and first trimester crown-rump length (Table S12).

3.4. Noise as mediator between natural spaces and the outcomes

Exposure to greenness was associated with lower total noise exposure (−1.92 dB [95%CI −2.44 to −1.40] per IQR increase in NDVI). We found that total noise exposure mediated 15% of the association between exposure to greenness and first trimester crown-rump length (natural indirect effect −0.01 [95% CI −0.03 to −0.00] and total effect: −0.11 SDS [95% CI −0.18 to −0.03]) (Fig. 4). No association was observed between distance to blue spaces and total noise exposure (0.34 dB [95%CI −0.25 to 0.73] per IQR increase in distance to blue spaces).

4. Discussion

In this population-based prospective cohort study, exposure to outdoor residential total noise (consisting of road traffic, railway, aircraft, and industry noise) and road traffic noise during pregnancy were associated with larger embryonic size in early pregnancy. These associations were not confounded or modified by traffic-related air pollution exposure. Total noise exposure during pregnancy mediated 15% of the association between exposure to greenness and embryonic size. No association was observed between distance to blue spaces and total noise exposure. Also, we found no evidence of an association between total noise or road traffic noise exposure during pregnancy and fetal growth or birth outcomes, nor between railway noise exposure during pregnancy and any of the outcomes.

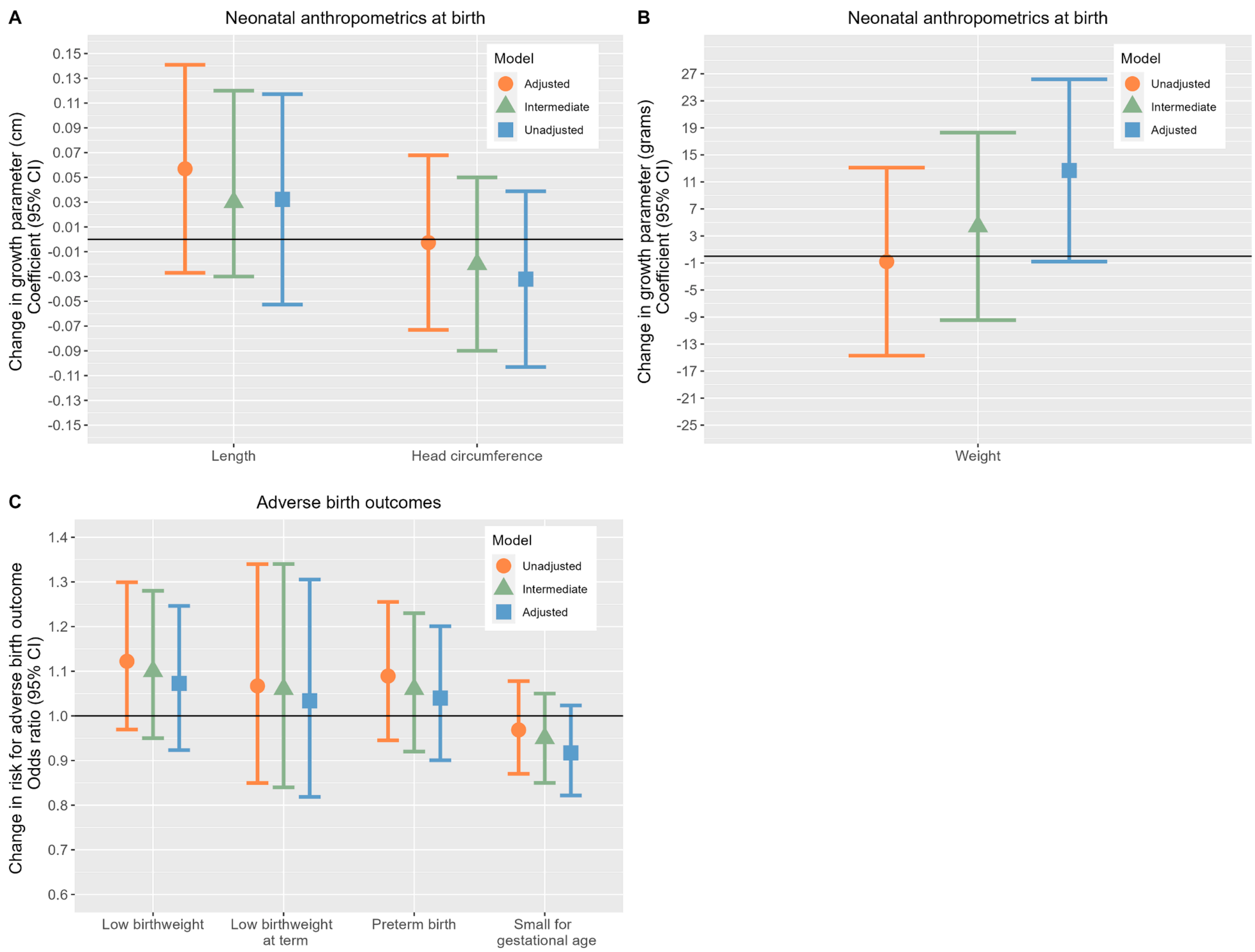


Unadjusted, minimally adjusted, and fully adjusted associations between a 10 dB increase in total noise exposure during pregnancy and embryonic size (crown-rump length) and fetal growth (head circumference, length, and weight). Coefficients and 95% confidence intervals of embryonic growth were obtained by univariate linear regression models and of fetal growth were obtained by linear mixed models. The minimally adjusted model was adjusted for maternal age at enrollment, maternal national origin, maternal educational level, monthly household income, residential greenness, and neighbourhood SES score. The fully adjusted model was additionally adjusted for periconceptional smoking, alcohol consumption during pregnancy, periconceptional folic acid use, parity and fetal sex. Abbreviations: dB, decibels; CI, confidence interval.

Fig. 2. Associations between a 10 dB increase in total noise exposure during pregnancy and embryonic size and fetal growth.

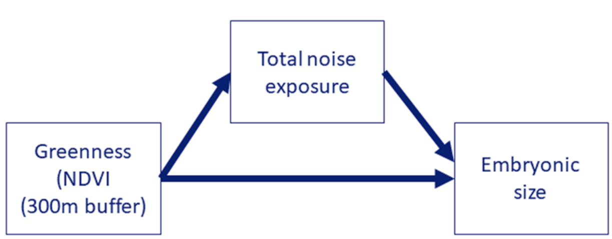
To the best of our knowledge no previous studies have examined the associations of environmental noise exposure during pregnancy with embryonic size and fetal growth parameters. In the present study we found that higher noise exposure during pregnancy was associated with larger crown-rump length in early pregnancy, while we did not find an association with fetal growth from mid-pregnancy until birth. This was a rather unexpected finding as our hypothesis was that adverse intra- and extrauterine exposures are associated with growth restriction across the entire pregnancy. Decelerated growth in the first trimester has been associated with adverse neonatal and childhood health outcomes.(Jaddoe et al., 2014; Mook-Kanamori et al., 2010) However, our findings are in line with recent studies in which other adverse exposures have also been associated with larger embryonic size.(Gootjes et al., 2019) The exact mechanisms behind these associations remain unclear, but it has been hypothesized that accelerated growth in the first trimester might be an instant survival mechanism of the embryo to adapt to adverse intrauterine conditions.(Fleming et al., 2018; Gluckman et al., 2008) For example, maternal stress, which might be caused by long-term exposure to noise, has been associated with epigenetic changes in DNA methylation. Amongst others, the hypomethylation of IGF2DMR has been related with an increased expression of embryonic growth hormones, and thus a larger embryonic size.(Kadakia and Josefson, 2016; Steegers-Theunissen et al., 2013; White et al., 2018; Zannas and Chrousos, 2017) Of note, the observed differences in our study were small, so the clinical implications of our findings might be limited at the individual level, but they can be more relevant from a population perspective. With limited literature available on noise exposure and embryonic size and fetal growth parameters, future studies including these outcomes are warranted to better understand why the embryo in early pregnancy might be more susceptible to noise exposure than the fetus.

The association between environmental noise exposure during pregnancy and different birth outcomes has been studied before. The absence of an association in our study is in line with previous literature. (Clark et al., 2020; Dzhambov and Lercher, 2019; Nieuwenhuijsen et al., 2019; Nieuwenhuijsen et al., 2017b; Smith et al., 2020) The most recent systematic reviews concluded that there was no evidence of an association between road traffic noise exposure and several birth outcomes. (Clark et al., 2020; Dzhambov and Lercher, 2019; Nieuwenhuijsen et al., 2017b) The review conducted by Nieuwenhuijsen et al. also took into account other sources of noise exposure besides road traffic noise exposure.(Nieuwenhuijsen et al., 2017b) They concluded that there was an association between aircraft noise and adverse birth outcomes.



Unadjusted, minimally adjusted, and fully adjusted associations between a 10 dB increase in total noise exposure during pregnancy and neonatal anthropometrics at birth (A and B) and risk for adverse birth outcomes (C). Coefficients (A and B) and odds ratios (C) and 95% confidence intervals were obtained by univariate linear regression models (A and B) and logistic regression models (C). The unadjusted models for neonatal anthropometrics at birth (A and B) were adjusted for gestational age at birth. The minimally adjusted model for all outcomes (A, B and C) was adjusted for maternal age at enrollment, maternal national origin, maternal educational level, monthly household income, residential greenness, and neighbourhood SES score. The fully adjusted model for all outcomes (A, B and C) was additionally adjusted for periconceptional smoking, alcohol consumption during pregnancy, periconceptional folic acid use, parity and fetal sex. Abbreviations: dB, decibels; CI, confidence interval; SES, socioeconomic status.

Fig. 3. Associations between a 10 dB increase in total noise exposure during pregnancy and neonatal anthropometrics at birth (A and B) and the risk for adverse birth outcomes (C).



	Estimate (95% CI) for an IQR (0.14) increase in average NDVI
Natural indirect effect	-0.01 (-0.03 to -0.00)
Natural direct effect	-0.09 (-0.17 to -0.02)
Total effect	-0.11 (-0.18 to -0.03)

Models were adjusted for maternal age at enrollment, maternal national origin, maternal educational level, monthly household income, periconceptional smoking, alcohol consumption during pregnancy, periconceptional folic acid use, parity, residential greenness, neighbourhood SES score, and fetal sex. Abbreviations: NDVI , Normalized Difference Vegetation Index; CI, confidence interval; IQR, interquartile range; SES, socioeconomic status.

Fig. 4. Mediation analyses between exposure to greenness during pregnancy, noise exposure during pregnancy, and embryonic size (N = 1527).

However, the studies on aircraft noise were mostly old and graded as very low quality due to not carefully considering confounding variables. Unfortunately, although we had information available from aircraft noise in our study, we were not able to conduct these specific analyses due to the relatively low proportion of women exposed to aircraft noise. Of note, studies on aircraft noise included populations exposed to high levels of noise (>75 dB). Although the European threshold for excess exposure is 55 dB L_{DEN} (European Environment Agency, 2017b), previous literature showed that average noise levels higher than 60 dB were associated with higher levels of cortisol, and thus a higher stress response.(Selander et al., 2009) In our study, half of the population had levels above 55 dB, a third had levels above 60 dB, and no one had levels above 75 dB. Thus, it could be possible that we did not have a large enough population exposed to high levels of noise to find associations between noise exposure and birth outcomes. More good quality research is needed to investigate the association of noise exposure in populations exposed to higher levels of noise with the growth of the embryo and the fetus.

Additionally, our results suggested that exposure to greenness was associated with smaller embryonic size, and that this association was partly mediated by a reduction of noise exposure. Previous studies did not explore the association between greenness exposure and embryonic growth specifically but did look at fetal growth across pregnancy and birth outcomes. A recent study in Spain found associations between higher exposure to residential greenness and larger femur length, biparietal diameter, and abdominal circumference across pregnancy including ultrasound measurements in the 1st, 2nd, and 3rd trimester. (Torres Toda et al., 2022) This was in line with a Chinese study also finding an association between higher exposure to residential greenness and larger biparietal diameter and abdominal circumference, and higher estimated fetal weight across pregnancy including ultrasound measurements of the three trimesters.(Lin et al., 2020) Two systematic reviews concluded that higher residential exposure to greenness was also associated with higher birth weight.(Akaraci et al., 2020; Hu et al., 2021) A few of the included studies considered noise exposure as a potential confounder, but none investigated the mediating effect of noise on the association between residential greenness and birth weight. Besides a reduction of noise exposure, another possible mechanism of the effects of exposure to greenness on embryonic growth in the first trimester may be higher physical activity (Nieuwenhuijsen et al., 2017a). Living in a green environment enables and supports physical activity.(Akaraci et al., 2020) Moreover, an inverse relationship between physical activity and fetal growth has been suggested.(Perkins et al., 2007) Although it has been shown that areas with more blue spaces have fewer sources of noise exposure (Dzhambov et al., 2018), distance to blue spaces was not associated with noise exposure in our study. Also, the evidence on the association between distance to blue spaces and birth outcomes is limited to very few studies that showed mixed results.(Akaraci et al., 2020) We did not observe an association between traffic-related air pollution and embryonic size. However, a recent systematic review and *meta*-analysis concluded that traffic-related air pollution was associated with low birth weight at term and being born small for gestational age.(Boogaard et al., 2022) Further research on traffic-related air pollution and surrounding natural spaces and their association with growth in early pregnancy are warranted.

The main strength of our study is its prospective design, with extensive ultrasound measures from early pregnancy until birth. This allowed us to explore both embryonic size and repeated fetal growth parameters from second trimester until birth instead of only using birth outcomes as proxies for fetal growth. Moreover, detailed information on outdoor noise exposure at the home address of the pregnant participant was available and accounted for the time living at the address in case of moving during pregnancy.

Our study also has some limitations that warrant consideration. First, there is the possibility of non-differential exposure misclassification since we only relied on outdoor average noise exposure data of the participants' home address. No information was available on noise exposure in occupational, indoor, or commuting settings. Individual measurement of noise exposure levels at multiple time points in pregnancy would give a more accurate and comprehensive estimation of the overall exposure to noise during pregnancy and would additionally enable the detection of a susceptible window of exposure. However, these are usually unfeasible in a large population study. Also, literature on noise exposure and hypertension indicates that noise exposure during the night is more relevant for the effect on the stress response than daytime noise.(Münzel and Sørensen, 2017) We expected pregnant women to be at home more often in the evening and night and therefore we considered the use of the L_{DEN} indicator as the most appropriate, covering noise exposure during the entire day with an emphasis on the evening and night as the most important contributors. Furthermore, we were not able to consider possible effect modifiers such as noise exposure at façade level, bedroom location of the mother, and noise sensitivity. Noise exposure levels are dependent on whether the bedroom has windows that face the street where the noise is assessed and in which level above the floor the bedroom is located. Having this additional information would have reduced the measurement error of our noise estimates, resulting in a more valid effect estimate. Furthermore, the level of noise that induces a physical response differs per individual and individuals exposed to the same noise level report divergent stress levels.(Tao et al., 2020) We applied inverse probability weighting to correct for selection bias and estimate unbiased inferences for the initial population in the cohort. However, we might have missed relevant information that explained the attrition in order to properly calculate the inverse probability weights and subsequently eliminate the entire bias. Lastly, although we adjusted for a large number of factors that have shown to be potentially associated with noise exposure and embryonic growth, residual confounding by other socio-economic or environmental factors cannot be discarded.

5. Conclusion

In conclusion, we observed that exposure to outdoor residential total noise (i.e., road traffic, railway, aircraft, and industry) and road traffic noise during pregnancy were associated with larger embryonic size. These associations were not confounded by traffic-related air pollution. Moreover, a reduction of total noise exposure during pregnancy partially mediated the association between exposure to greenness and smaller embryonic size. No association was observed between distance to blue spaces and embryonic size. We did not find an association between total or road traffic noise exposure during pregnancy with fetal growth nor with birth outcomes, or with railway noise exposure and any of the outcomes. Additional research is warranted to confirm and further understand the potential effects of noise exposure during pregnancy on altered embryonic growth, including other urban environmental exposures such as traffic-related air pollution and natural spaces.

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CRediT authorship contribution statement

Naomi Graafland: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft. **Esmée Essers:** Methodology, Validation, Writing – review & editing. **Anke Posthumus:** Writing – review & editing. **Dionne Gootjes:** Formal analysis, Writing – review & editing. **Albert Ambrós:** Methodology, Data curation. **Eric Steegers:** Writing – review & editing, Funding acquisition, Supervision. **Mònica Guxens:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

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

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107730.

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