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FULL RESEARCH PAPER
Air pollution and environmental science

Prenatal particulate air pollution exposure predicts arterial stiffness in childhood

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Aims Early-life environment is crucial for foetal programming and later-life development. Exposure to particulate air pollution during gestation may increase the risk of cardiovascular diseases (CVD) later in life. We investigated the association between exposure to $PM_{2.5}$ (particulate matter with a diameter of 2.5 μm or less) during gestation and pulse wave velocity (PWV) in children.

Methods and results In the prospective ENVIR*ON*AGE (ENVIRonmental influence *ON* early AGEing) birth cohort (Belgium), mother–child pairs were recruited at birth, and 244 children between 9 and 11 years were followed up. Arterial stiffness was assessed using carotid-femoral PWV via the Vicorder® (Skidmore Medical, Bristol, UK). A high-resolution spatiotemporal model was used to model daily prenatal and postnatal $PM_{2.5}$ exposure levels. Associations between prenatal $PM_{2.5}$ exposures and PWV were tested using linear regression models followed by fitting weekly prenatal exposures to distributed lag non-linear models (DLNM). Among the 244 children [132 girls (54.1%); mean (S) age, 10.2 (0.8) years], a 5 $\mu g/m^3$ increment in prenatal $PM_{2.5}$ exposure during trimester two was significantly associated with a 0.09 m/sec higher PWV (95% CI, 0.01 to 0.17; $P = 0.03$). Accounting for entire childhood $PM_{2.5}$ exposure, $PM_{2.5}$ exposure during trimester two remained a predictor of PWV (0.08 m/sec, 95% CI: −0.0006 to 0.16; $P = 0.05$).

Conclusion PWV is an independent predictor of future CVD and all-cause mortality in the general population. Therefore, associations of air pollution exposure during gestation with childhood PWV highlight the potential long-term consequences on the child's cardiovascular system from early life onwards.

Lay summary The association between exposure to $PM_{2.5}$ (particulate matter with a diameter of 2.5 μm or less) during gestation and pulse wave velocity (PWV) in children was studied.

- We found that maternal exposure to higher levels of $PM_{2.5}$ during the second trimester of gestation was significantly associated with increased PWV in their children during childhood.
- Exposure during weeks 16 to 18 of gestation was identified by distributed lag non-linear models (DLNMs) as the potential exposure windows of vulnerability in association with PWV 10 years later.

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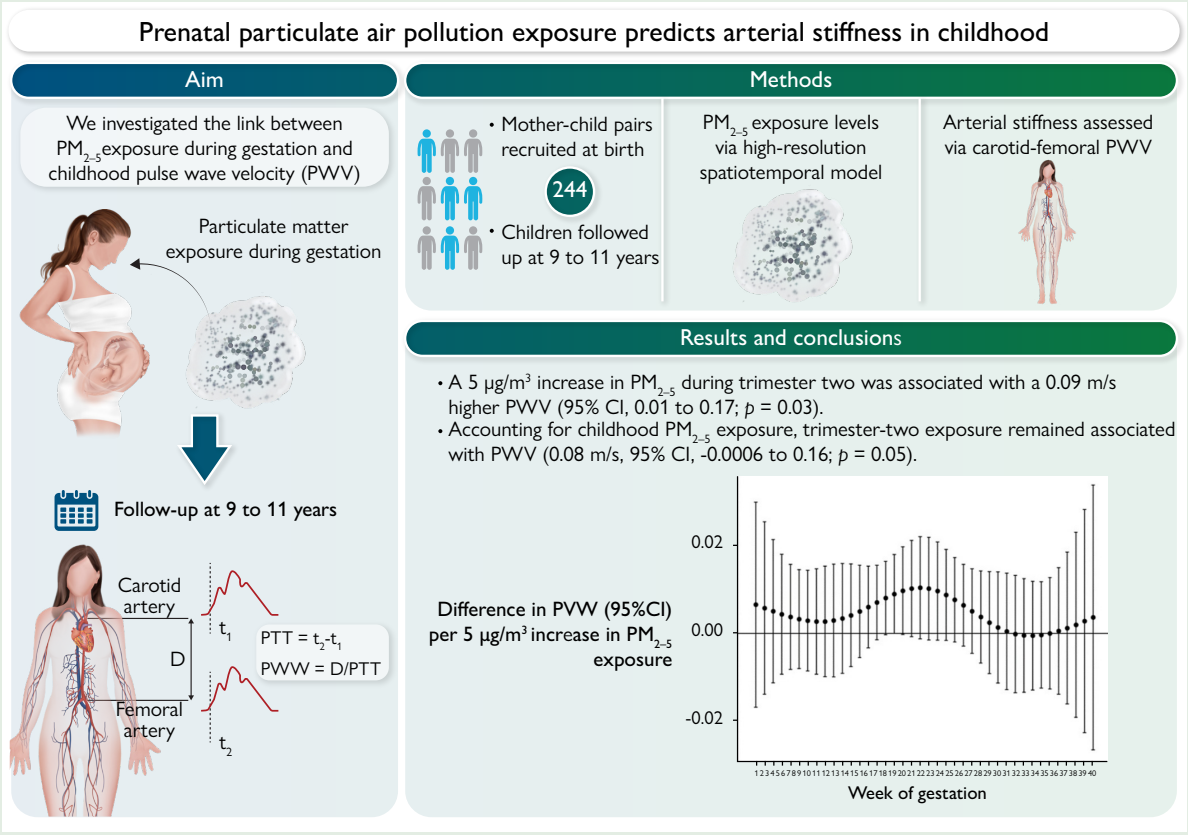
Graphical Abstract



Keywords ENVIRONAGE • Prenatal • Air pollution • Arterial stiffness • Pulse wave velocity

Introduction

Despite all efforts to improve air quality in the past decades, air pollution remains the biggest environmental health risk factor affecting human health, even before birth.[1] Research indicates that ultrafine particles present in air pollution can enter the bloodstream and have the capability to cross the placental barrier.[2,3] Air pollution particles reaching the developing foetus can pose risks to both foetal development and long-term health outcomes, as studies have shown that $PM_{2.5}$ exposure during gestation is associated with mid-gestation maternal[4] and placental inflammation,[5] resulting in adverse birth outcomes such as stillbirth,[6] low birth weight,[7] and preterm birth.[8]

Arterial stiffness is a significant indicator of changes in the vascular structure and a reliable predictor of the development of cardiovascular diseases (CVD).[9] Degenerative alterations in the inner layer of large elastic arteries are a natural consequence of aging, reducing arterial elastin content, and increasing arterial stiffness.[10] However, evidence suggests that the disease process can already start early in life. Studies reported that prenatal air pollution exposure has been associated with increased arterial stiffness in children under 9 years[11] and in adolescents,[12] meaning that arterial stiffness may manifest in early childhood.

Whether alterations in arterial stiffness during childhood can indicate CVD risk in adulthood is still uncertain. Nevertheless, evidence indicates a strong association between blood pressure and arterial stiffness in children and adolescents.[13] These data suggest that elevated childhood blood pressure can persist over time and subsequently increase the risk of CVD later in life.[14]

We hypothesized that children between 9 and 11 years might have a higher pulse wave velocity (the golden standard to measure arterial stiffness) when exposed to higher $PM_{2.5}$ (particulate matter with a diameter of 2.5 µm or less) exposure before birth.

Methods

Study population

Mother–child pairs were enrolled in the ENVIRonmental Influence *ON* early Ageing study (ENVIR*ON*AGE), an ongoing prospective birth cohort. Data collection and study procedures have been described previously.[15] The study complies with the Helsinki Declaration, and study protocols of recruitment and follow-up phases were approved by the ethics committees of East-Limburg Hospital in Genk and Hasselt University (reference no. B371201216090 and B1152021000007). Participants were recruited on arrival for delivery at the East-Limburg Hospital in Genk (Belgium) from February 2010 onwards, currently including more than 2200 mother–child pairs. Mothers provided written informed consent at birth and follow-up.

A follow-up occurred when the child was 9–11 years old, from July 2021 to January 2024. 761 children were aged 9–11 years old between July 2021 and January 2024. However, 221 participants had previously indicated they would no longer participate in a follow-up examination. 174 could not be contacted due to outdated contact details, and eight were ineligible for participation since they had moved away. Of the 358 contacted, 78 participants

did not give consent, and 19 did not show up. Finally, 261 participants participated in the follow-up study (i.e. a final participation rate of 72.9%). Children with missing pulse wave velocity (PWV) data ($n = 17$) were excluded from the analysis. A total of 244 children were included in this study. Details on the inclusion are presented in the flow chart in Supplementary material online, *Figure S1*. Compared with the baseline sample, there were no differences with regard to sex ($P = 0.18$), gestational age ($P = 0.17$), birth weight ($P = 0.97$), maternal pre-pregnancy body mass index (BMI) ($P = 0.64$), gestational diabetes ($P = 0.16$) and gestational hypertension ($P = 0.48$), but the follow-up sample included more highly educated mothers (72.5% vs. 43.1%) and had a lower percentage of mothers who smoked during pregnancy (8.6% vs. 16.2%).

Study population measures

During the first antenatal visit (weeks 7–9 of gestation), the gestational age was estimated based on the mother's last menstrual period and ultrasonography. Perinatal parameters (i.e. date of birth, newborn sex, and birth weight) and information on maternal pre-pregnancy BMI, calculated as weight in kilograms divided by height in metres squared, history of gestational diabetes, hypertension, and preeclampsia were collected from medical records. After delivery, mothers completed questionnaires about their health and lifestyle, residential address(es), maternal education before and during, and smoking status before and during pregnancy. Maternal education was categorized per ISCED guidelines[16] as 'low' (no diploma or primary school degree), 'middle' (secondary school degree), or 'high' (college or university degree). Occupation was classified according to the International Standard Classification of Occupations. We chose not to ask participants about personal income, as prior experience in Belgian population-based studies has shown that such questions are often perceived as a violation of privacy.[17,18] In addition to the individual-level socioeconomic indicators, we also determined neighbourhood income (median annual household income) using the participants' residential addresses, as this might reflect contextual associations and the geographical dispersion of potential risk factors.[19] These were linked to statistical sectors, the smallest administrative units with available statistical data from the Belgian National Institute of Statistics. Participants lived in 170 different statistical sectors. The median household income is derived from 2022 tax records, including taxable sources such as employment income, pensions, dividends, cadastral income, and maintenance payments. It excludes non-taxable income, such as patient benefits and integration income. We also incorporated the Belgian Indices of Multiple Deprivation (BIMDs), which measure relative deprivation across Belgium's smallest geographical unit (the statistical sector).[20] The indices rank areas into deciles from most to least deprived. BIMDs combine six domains: income, employment, education, housing, health, and crime, each built from relevant local indicators. These domains are merged into an overall deprivation score per sector. Maternal smoking was defined as 'never smoked', 'former smoker' when the mother had quit smoking before pregnancy, and 'current smoker' when smoking continued during pregnancy.

Participants were invited for a follow-up visit after 9–11 years at the university's examination centre. Mothers completed questionnaires about their child's health and lifestyle conditions. Trained research staff performed anthropometric and cardiovascular measurements. The child's height was measured using a stadiometer with a precision of 0.5 cm, and body weight was recorded to the nearest 0.1 kg using a digital scale. The waist circumference was rounded to the nearest 0.1 cm. Blood pressure measurements were performed using a standardized method described by the European Society of Hypertension.[21] The child's blood pressure was measured using the automated Omron HBP-1320 (oscillometric device Omron Healthcare Co., Ltd., Kyoto, Japan), with five consecutive measurements taken at one-minute intervals. Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were derived by averaging the last three measurements. Mean arterial pressure (MAP) was defined as (2DBP + SBP)/3. Information on postnatal household smoking (i.e. child exposure to second-hand smoke) was collected (absent when none of the parents smoked in the house and present when at least one parent smoked in the house).

Pulse wave velocity

Carotid-femoral pulse wave velocity (CFPWV) represents the most frequently used PWV measure for clinical and prognostic applications,[22] showing excellent reliability.[23] PWV refers to the velocity of the forward-traveling pressure pulse waves generated by the systolic contraction of the heart to travel along the arterial tree. Elevated PWV values signify increased vascular stiffness, contributing to a more rigid arterial circulation and subsequent cardiac remodelling.[24] PWV was measured via the Vicorder® (Skidmore Medical, Bristol, UK), an oscillometric device to detect pulse waveforms between two recording sites. PWV value was obtained in metres per second (m/sec) after a minimum of eight consecutive stable waveforms, and mean values were used for further analysis. Briefly, the child was in a supine position, with the head and shoulders elevated by 30°, so the skin and muscles over the carotid artery were relaxed. A small cuff containing an inflatable cushion was placed around the neck above the right common carotid artery, and a larger cuff was placed around the right thigh. After inflating both cuffs to the automatically set value, pulse waves from the carotid and femoral arteries were captured. Transit time (TT) was calculated by cross-correlating pulse waves at the carotid and femoral sites. The path length was determined by measuring the horizontal distance between the suprasternal notch and the centre of the femoral cuff using a measurement tape with an accuracy of 0.5 cm. PWV was computed as the path length divided by TT.

Air pollution exposure assessment

During gestation, outdoor $PM_{2.5}$ concentrations (in $\mu g/m^3$) were determined using a validated interpolation method (kriging), which operates at a high spatial and temporal resolution.[25] This method incorporates the residential addresses and integrates air pollution data from fixed-site monitoring stations, land cover data derived from satellite images (Corine land cover data set), and a dispersion model. This model chain provides interpolated air pollution values on a dense, irregular receptor point grid coupled with a dispersion model that uses emissions from point and line sources.[26,27] More than 80% ($R^2 = 0.8$) of the temporal and spatial variability in $PM_{2.5}$ concentrations in the Flemish region of Belgium was explained by this interpolation tool.[28] Ultrasound imaging data combined with the first day of the mother's last menstrual period were used to estimate the date of conception.[29] Daily $PM_{2.5}$ concentrations were averaged over the entire gestation and for each trimester: 1–13 weeks (trimester one), 14–26 weeks (trimester two), and 27 weeks to delivery (trimester three). Based on daily $PM_{2.5}$ exposure, we calculated the weekly mean $PM_{2.5}$ concentrations of gestational weeks one to 40, with week one starting from the estimated date of conception. If the gestational age was less than 40 weeks, $PM_{2.5}$ exposure levels after delivery until week 40 were set to zero.

Postnatal $PM_{2.5}$ exposures were averaged for one week and one month before follow-up as short-term exposure windows, and the mean exposure during childhood (i.e. the mean daily exposure from birth until the day before follow-up) as a long-term exposure window. Address changes were considered during ($n = 20$; 8.2%) and after pregnancy ($n = 23$; 9.4%). The Royal Meteorological Institute of Belgium provided the daily outdoor mean temperature using the data obtained at the Diepenbeek (Belgium) measuring station.

Statistical analysis

Data was analysed using Rstudio (version 4.2.2; Core Team, Vienna, Austria). Study population characteristics are expressed as means (SDs) or numbers (percentages). Correlations between prenatal $PM_{2.5}$ exposure and childhood PWV were assessed by Pearson correlation.

Associations between prenatal $PM_{2.5}$ exposure and childhood PWV were investigated with multivariable linear regression models. Trimester-mean $PM_{2.5}$ exposure levels were entered into the same model

to estimate independent trimester-specific effects. The model was adjusted for *a priori* selected covariates: sex, gestational age (weeks), birth weight (grams), age (years), mean heart rate, MAP, waist circumference, height, and weight of the child, mean outdoor temperature on the day of follow-up, educational level before and during pregnancy, and smoking of the mother before and during pregnancy. Adjustment for mean outdoor temperature was implemented to account for the potential influence of seasonal effects. The threshold for statistical significance was set at a 95% confidence level ($P < 0.05$). Q–Q plots evaluated the normality of the residuals. The magnitude of all associations was expressed for a 5 μg/m^3 increment in the observed $PM_{2.5}$ exposure.

We tested the consistency and further identified potential exposure windows of vulnerability of the initial findings by applying a distributed lag non-linear model (DLNM). In the DLNM, the exposure–response relationship and lag–response relationship are simultaneously involved in one model, via the construction of a cross-basis combining two basis functions corresponding to exposure structure and lag structure, respectively. Based on a previous study, in our analysis, we assumed a linear exposure-response function and modelled the lag structure using a natural cubic spline with five degrees of freedom (df), setting three knots at equally spaced values along the original lag scale (1–40 weeks).[30] Estimates were presented as the difference with 95% CI in childhood PWV for a 5 μg/m^3 increment in the observed $PM_{2.5}$ exposure at each gestational week. Adjustments employed as in the previous regression models, with the exception of trimester-specific exposures, remained consistent.

In a secondary analysis, we investigated the associations between postnatal $PM_{2.5}$ exposure and childhood PWV with linear regression models for one week and one month before the follow-up visit and the entire childhood. The model was adjusted for the same covariates.

Lastly, we performed a sensitivity analysis to evaluate the robustness of our models. We adjusted the main model separately for postnatal exposures (i.e. postnatal $PM_{2.5}$ exposure one week before follow-up visit, postnatal $PM_{2.5}$ exposure one month before follow-up visit, postnatal $PM_{2.5}$ exposure entire childhood period), gestational diabetes, hypertension, preeclampsia, maternal pre-pregnancy BMI, postnatal household smoke, neighbourhood household income, neighbourhood deprivation, and home ownership. The magnitude of all associations was expressed for a 5 μg/m^3 increment in the observed $PM_{2.5}$ exposure.

Results

Study population characteristics

Characteristics of the 244 included participants are provided in *Table 1*. The children, including 132 [54.1%] girls, had a mean (SD) birth weight of 3403.5 (464.7) g and a mean gestational age of 39.1 (1.6) weeks. The mothers had a mean (SD) age of 30.2 (4.1) years during pregnancy. Most mothers had a college or university degree [177 (72.5%)] and never smoked [171 (70.1%)]. Follow-up visits were spread over all seasons, with a slightly higher number of visits during summer [82 (33.6%)]. The mean outdoor temperature was 12.3°C (and ranged from −0.8 to 23.8°C). The children had a mean age of

Table 1 General characteristics of the participants at birth and the follow-up visit

Characteristic	Participants, No. (%) ($n = 244$)
Birth	
Sex	
Girls	132 (54.1)
Birth weight, mean (SD), g	3403.5 (464.7)
Gestational age, mean (SD), wk	39.1 (1.6)
Follow-up visit	
Season of follow-up visit	
Winter	51 (20.9)
Spring	55 (22.5)
Summer	82 (33.6)
Autumn	56 (23.0)
Temperature at follow-up visit, mean (SD), °C	12.3 (5.8)
Age at follow-up, mean (SD), y	10.2 (0.8)
Measurement at follow-up, mean (SD)	
Waist circumference, cm	63.1 (8.6)
Height, cm	142.6 (7.8)
Weight, kg	36.8 (8.8)
Blood pressure, mean (SD), mmHg	
Systolic	108.9 (10.2)
Diastolic	66.0 (6.6)
Mean arterial	82.2 (7.3)
Heart rate, mean (SD), beats/min	70.8 (8.4)
Pulse wave velocity, mean (SD), m/sec	5.1 (0.7)
Postnatal household smoke	
Yes	29 (12.4)
No	205 (87.6)
Mother	
Maternal age during pregnancy, mean (SD), y	30.2 (4.1)
Maternal pre-pregnancy BMI, mean (SD)	24.4 (4.6)
Maternal educational level[a]	
Low	8 (3.3)
Middle	59 (24.2)
High	177 (72.5)
Maternal smoking status[b]	
Never smoker	171 (70.1)
Former smoker	52 (21.3)
Current smoker	21 (8.6)
Gestational diabetes	
Yes	14 (5.7)
No	230 (94.3)
Gestational hypertension	
Yes	7 (2.9)
No	237 (97.1)
Preeclampsia	
Yes	1 (0.4)
No	243 (99.6)

BMI, body mass index (calculated as weight in kilograms divided by height in metres squared)
[a]Maternal educational level was 'low' when no diploma was obtained, 'middle' when a high school diploma was obtained, and 'high' when a college or university diploma was obtained.
[b]Maternal smoking status was categorized as 'never smoker', 'former smoker' when quitted smoking before pregnancy, and 'current smoker' when smoking continued during pregnancy

10.2 (0.8) years and a waist circumference of 63.1 (8.6) cm at follow-up. The mean height and weight were 142.6 (7.8) cm and 36.8 (8.8) kg, respectively. The children had a mean heart rate of 70.8 (8.4) beats/min and MAP of 82.2 (7.3) mmHg. The mean PWV was 5.1 (0.7) m/sec, ranging from 3.5 to 7.0 m/sec.

Exposure characteristics

The mean $PM_{2.5}$ exposure for the included participants [interquartile range (IQR)] during the entire gestation was 14.1 (11.7–16.1) $\mu g/m^3$ (see Supplementary material online, Table *S1*). A mean $PM_{2.5}$ exposure of 14.1 (9.5–18.2) $\mu g/m^3$ was calculated for the first, 14.1 (9.7–17.8) $\mu g/m^3$ for the second, and 14.0 (9.4–17.6) $\mu g/m^3$ for the third trimester of gestation. For childhood $PM_{2.5}$ exposures, a mean $PM_{2.5}$ exposure of 9.1 (6.0–10.8) $\mu g/m^3$ was calculated for one week and 10.0 (7.3–12.1) $\mu g/m^3$ for 1 month before follow-up. The mean $PM_{2.5}$ exposure during the entire childhood was 11.0 (10.4–11.9) $\mu g/m^3$.

Association between prenatal $PM_{2.5}$ Exposure and Childhood Pulse Wave Velocity

Exposure to $PM_{2.5}$ during the entire gestation and trimester two was positively associated with childhood PWV (*Figure 1*). In the unadjusted model, a 5 $\mu g/m^3$ increment increase in $PM_{2.5}$ exposure during the entire gestation and trimester two was associated with a 0.20 (0.04 to 0.35; $P = 0.01$) and a 0.10 m/sec (95% CI, 0.01 to 0.18; $P = 0.02$) higher childhood PWV, respectively (*Table 2*).

Childhood PWV increased with the MAP (regression coefficient ± SE, 0.02 ± 0.006 m/sec/mmHg; $P = 0.003$), height of the child (0.02 ± 0.009 m/sec/cm; $P = 0.006$), and mean outdoor temperature on the day of follow-up (0.02 ± 0.007 m/sec/°C; $P = 0.0008$). Other potential confounders and covariates were kept in the model but were not statistically significant (see Supplementary material online, Table *S2*).

In the adjusted model, higher $PM_{2.5}$ exposure during trimester two was significantly associated with a higher childhood PWV. For every 5 $\mu g/m^3$ increment increase in $PM_{2.5}$ exposure during trimester two,

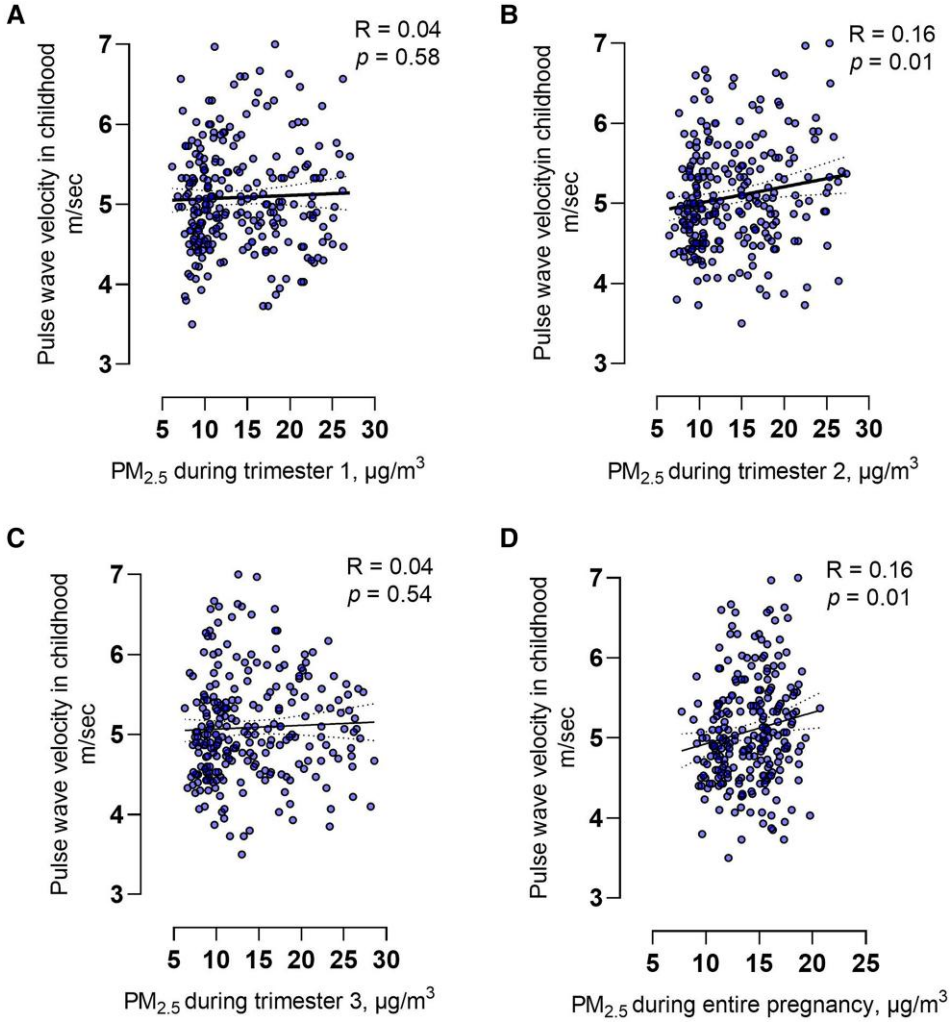


Figure 1 Scatterplot illustrating the relationship between $PM_{2.5}$ exposure during the different trimesters (*A, B*, and C), the entire gestation (*D*), and childhood pulse wave velocity. *Abbreviation:* $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 µm or less. *R* represents the Pearson correlation coefficient. Regression lines (solid black) are shown with 95% CI (black dashed line).

Table 2 Association between prenatal $PM_{2.5}$ exposure ($\mu g/m^3$) and childhood pulse wave velocity ($n = 244$)

	Unadjusted model		Adjusted model	
Exposure window	**Difference (95% CI), m/sec**	***P* value**	**Difference (95% CI), m/sec**	***P* value**
Entire gestation	0.20 (0.04 to 0.35)	0.01	0.10 (−0.07 to 0.26)	0.26
Trimester 1	0.03 (−0.06 to 0.13)	0.48	−0.02 (−0.12 to 0.08)	0.69
Trimester 2	0.10 (0.01 to 0.18)	0.02	0.09 (0.01 to 0.17)	0.03
Trimester 3	0.02 (−0.04 to 0.12)	0.59	−0.06 (−0.16 to 0.03)	0.20

$PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.
Estimates are presented as the difference [with 95% confidence interval (CI)] in pulse wave velocity (m/sec) for a 5 $\mu g/m^3$ increment increase in $PM_{2.5}$ during the entire gestation and all the trimesters. In the unadjusted model, trimester-specific $PM_{2.5}$ exposures were mutually adjusted for the other gestational exposure windows to estimate the independent effect of each trimester of exposure. The adjusted model was adjusted for exposure to $PM_{2.5}$ during other trimesters, sex, gestational age, birth weight, age, mean heart rate, mean arterial pressure, height, weight, and waist circumference of the child at follow-up, mean outdoor temperature at follow-up, maternal educational level, and smoking before and during pregnancy.

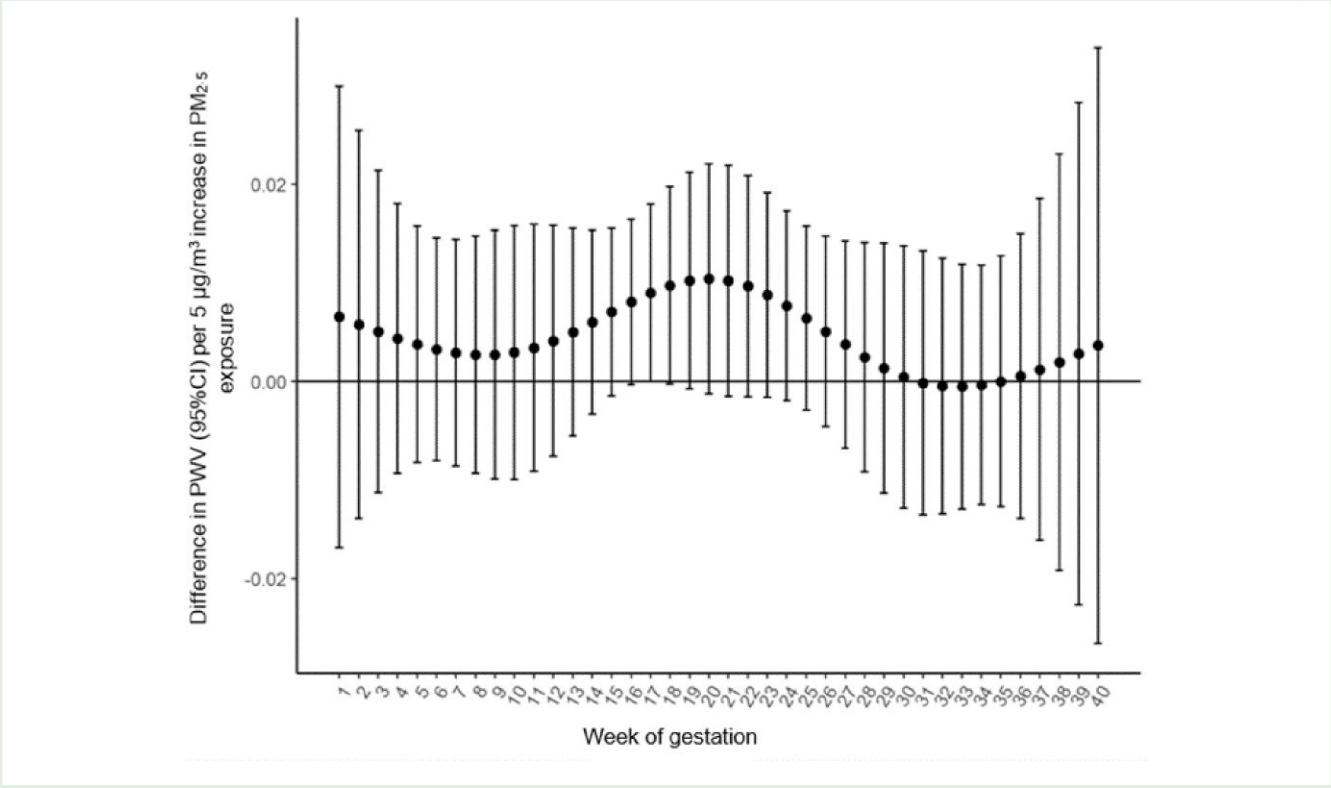


Figure 2 Association between week-specific prenatal $PM_{2.5}$ Exposure ($\mu g/m^3$) and Childhood Pulse Wave Velocity (PWV). Week-specific estimates were provided as the difference [with 95% confidence interval (CI)] in pulse wave velocity (m/sec) for a five $\mu g/m^3$ increment of $PM_{2.5}$ exposure. Models were adjusted for sex, gestational age, birth weight, age, mean heart rate, mean arterial pressure, height, weight, and waist circumference of the child at follow-up, mean outdoor temperature at follow-up, maternal educational level, and smoking before and during pregnancy. $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

a 0.09 m/sec higher childhood PWV (95% CI, 0.01 to 0.17 m/sec; $P = 0.03$) was found. No significant changes were found in the other time windows (*Table 2*).

Furthermore, lag-specific (weekly) DLNM estimations of the association between prenatal $PM_{2.5}$ exposure and childhood PWV are presented in *Figure 2*. Potential exposure windows of vulnerability were visually apparent during weeks 16 (0.01 m/sec, 95% CI: −0.0003 to 0.016; $P = 0.06$), 17 (0.01 m/sec, 95% CI: 0.000001 to 0.018; $P = 0.05$), and 18 (0.01 m/sec, 95% CI: −0.0003 to 0.02; $P = 0.06$) of gestation.

Secondary analysis

Results for the association between postnatal $PM_{2.5}$ exposure and childhood PWV are presented for both unadjusted and adjusted models in the Supplement (see Supplementary material online, Table *S3*). In

the unadjusted model, $PM_{2.5}$ exposure 1 week before the follow-up visit was significantly associated with a 0.13 m/sec (95% CI, −0.23 to −0.04, $P = 0.004$) lower childhood PWV. However, this association did not remain significant after adjustment.

Sensitivity analyses

We tested the robustness of our findings with several sensitivity analyses (see Supplementary material online, Table S4) and evaluated the potential influence of extreme values by conducting diagnostic analyses, including Cook's distance. This allowed us to identify and account for any influential observations. The results of the sensitivity analysis indicated that the observed associations were not driven by individual data points with high leverage. The observed associations between $PM_{2.5}$ exposure during trimester two and childhood PWV remained significant after additional adjustment for postnatal exposure during different time windows (short-term and long-term), showing that prenatal $PM_{2.5}$ exposure and childhood PWV were independent of $PM_{2.5}$ exposure during childhood.

Discussion

The key findings of this study can be summarized as follows: (i) PWV of children aged 9–11 years increased with a higher prenatal $PM_{2.5}$ exposure during trimester two, with potential exposure windows of vulnerability during weeks 16, 17, and 18 of gestation, and (ii) $PM_{2.5}$ exposure during trimester two remained significantly associated with childhood PWV after additional adjustment for different postnatal $PM_{2.5}$ exposures.

Exposure to air pollutants is a global concern, and several studies have already demonstrated that $PM_{2.5}$ exposure can increase risks of cardiovascular diseases, especially in vulnerable populations.[31] In our study, we identified mid-gestation as a potential exposure window of vulnerability linking prenatal air pollution with childhood PWV, aligning with key placental developments. Early in pregnancy, the placental barrier is thick and poorly perfused, but by week 10, it thins, and fetal capillary networks expand, enhancing maternal–fetal exchange and potentially increasing fetal susceptibility to environmental exposures.[32] Telomere length, a marker of biological ageing, is well-documented in relation to the development of cardiovascular diseases.[33] Previously, we found that lower telomere length at birth was associated with higher $PM_{2.5}$ exposure during trimester two.[34] The PROGRESS study showed that prenatal exposure to $PM_{2.5}$, especially during the second and third trimesters, was associated with higher systolic and diastolic blood pressure in children aged 4–6 years, highlighting mid-gestation as a potential exposure window of vulnerability for blood pressure programming.[35]

In the literature, studies conducted in children and young adults found comparable results for the association between air pollution exposure and arterial stiffness. One study found that prenatal $PM_{2.5}$ and PM_{10} exposures are associated with higher carotid arterial stiffness in college students.[12] They reported that a two SD increase in prenatal $PM_{2.5}$ exposure was associated with a 5% increase in carotid stiffness index beta, a 5% increase in Young's elastic modulus, and a 5% decrease in distensibility. Also, they evaluated prenatal and postnatal $PM_{2.5}$ in mutually adjusted models and found that the effects of $PM_{2.5}$ on carotid arterial stiffness were likely due to prenatal rather than postnatal exposure. Another study in young people reported a 4.1% higher PWV associated with a 25 $\mu g/m^3$ increase in nitrogen dioxide (NO_2) levels and a 5.3% increase with a 5 $\mu g/m^3$ increase in sulphur dioxide (SO_2) over a lifetime.[36] In a study involving 52 Italian children, associations between living closer to a main road and higher carotid arterial stiffness were observed compared to those living further away.[37] The observed mean PWV values in our cohort were comparable to published reference values for children of similar age,[38] which provides context for the absolute values. Furthermore, intra- and interobserver repeatability of the PWV measured with the Vicorder device was compared with PWV values using the SphygmoCor system by several studies. PWV measured with the Vicorder device was, on average, highly correlated with PWV values measured with the SphygmoCor system.[39] However, it is important to note that this similarity does not imply validation of our findings or confirm clinical relevance. The observed associations between prenatal $PM_{2.5}$ exposure and PWV should always be interpreted within the context of effect sizes and biological plausibility rather than the absolute PWV values alone.

The current World Health Organization's (WHO) air quality guidelines suggest that the annual and 24-hour mean $PM_{2.5}$ concentration should be below 10 $\mu g/m^3$ and 25 $\mu g/m^3$, respectively.[40] However, despite improved air quality levels in Europe, measurements show levels exceeding the recommended thresholds. Moreover, studies have reported alarming results, indicating that adverse effects of air pollution may already occur at lower air pollution concentrations than the current guidelines.[41] Our cohort observed $PM_{2.5}$ concentrations during gestation and childhood were 14.1 $\mu g/m^3$ and 11.0 $\mu g/m^3$, respectively. Comparing these concentrations with current WHO guidelines, our cohort's gestation and childhood $PM_{2.5}$ concentrations exceed the WHO's recommended annual mean $PM_{2.5}$ thresholds, suggesting potential cardiovascular health risks.

The 'Developmental Origins of Health and Diseases' concept highlights that exposures during critical periods of development can have long-term effects on health outcomes later in life.[42,43] While cardiovascular events and diseases are uncommon in young children, early life changes to the circulatory system might raise the risk of acquiring these harmful conditions, which can progress silently until clinical signs appear. Evidence from autopsy studies suggests that lipid accumulation in the artery wall during childhood initiates the development of atherosclerosis and results in fatty streaks.[44,45] As the PWV is a non-invasive measurement and an independent predictor of future CVD events and all-cause mortality, this is a reliable measurement to identify populations at risk for adverse cardiovascular outcomes and indicate early atherosclerosis stages before clinical symptoms emerge. Studies in adults have found that elevated PWV has been shown to increase the risk of adverse cardiovascular outcomes significantly. They reported that an increase in PWV by one m/sec corresponds to a 14%, 15%, and 15% increase in the risk of total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively.[46] PWV may be tracked from childhood into adulthood in a manner similar to blood pressure. Evidence suggests that early-life vascular changes can persist over time, with higher PWV in childhood associated with elevated cardiovascular risk later in life. Similarly, childhood blood pressure levels have been shown to predict adult hypertension,[47] and elevated PWV in early life may reflect early vascular aging and contribute to the development of long-term vascular risk. This tracking underscores the importance of identifying and mitigating early-life exposures that influence vascular function.

This research has both strengths and limitations. A first strength is that we were able to derive accurate estimates of the impact of air pollution exposure on PWV in children via data collection at birth and follow-up. Furthermore, we measured the carotid-femoral PWV, the golden standard for non-invasive arterial stiffness assessment and

cardiovascular health, showing excellent reliability.[23] We used weekly average exposures corresponding to each gestational week instead of averaging exposures over each trimester and employed them in DLNMs. This enabled us to identify potential exposure windows of vulnerability per gestational week. Using a high-resolution exposure model allowed us to integrate daily exposure concentrations of air pollutants at the mothers' home addresses into weekly exposure estimates throughout gestation. Also, we were able to adjust for important potential confounders, and the sensitivity analyses showed minimal changes to the observed associations, indicating robust and consistent results. However, while elevated PWV is predictive of future cardiovascular risk, our findings warrant confirmation in longitudinal studies with clinical cardiovascular outcomes. Although our results were consistent after adjustments, the risk of confounding by possible unknown factors associated with $PM_{2.5}$ exposure during gestation and childhood PWV cannot be excluded. Another limitation of our study is that the sample size was relatively small, and the population characteristics show that we are losing families with relatively lower socioeconomic statuses (SES) during follow-up. We acknowledge that the effect size of $PM_{2.5}$ exposure on childhood PWV appears modest. However, it is important to note that even small increases in risk can have a substantial impact when the exposure is common. While the effect on the individual level appears modest, the population-level impact could be large, especially in settings with high ambient $PM_{2.5}$ levels. Moreover, similar small effect sizes have been reported in other environmental epidemiology studies, reflecting the complex and multifactorial origin of disease development. These small shifts in PWV, when combined with other risk factors, may cumulatively contribute to increased long-term cardiovascular risk. Another limitation is the potential misclassification of exposure. Our results are based on daily levels of residential outdoor air pollution exposure during prenatal and postnatal life, which do not account for indoor pollution levels or personal exposure in other environments, such as work or school. Although our exposure models are based on residential particulate matter during prenatal and postnatal life, the accuracy of our exposure models and relevance for personal and internal exposure have been supported since residential air pollution levels during pregnancy of mothers within the ENVIRONAGE birth cohort correlated with the placental and cord blood carbon load.[3]

Conclusion

This study presents evidence that prenatal $PM_{2.5}$ exposure is associated with higher childhood PWV. Our results contribute to the understanding of the potentially important role of PWV in the association between gestational exposure to air pollution and the potential tracking of cardiovascular diseases later in life.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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