



Prenatal exposure to PM_{2.5} constituents and newborn leukocyte telomere length in a prospective study: Windows of susceptibility and modification by maternal folic acid supplementation

Gaojie Fan ^{a,b}, Qing Liu ^{a,b}, Qing Fang ^{a,b}, Fei Luo ^{a,b}, Xiaofeng Huang ^{a,b}, Heng Li ^{a,b}, Wenwen Guo ^{a,b}, Binghai Liu ^{a,b}, Lianyan Yan ^{a,b}, Liqin Hu ^c, Chao Xiong ^c, Zhongqiang Cao ^c, Xi Chen ^b, Zitong Chen ^d, Jing Wei ^e, Youjie Wang ^{a,b}, Xiaoning Lei ^{d,*}, Lulu Song ^{a,b,**,1}

^a Department of Maternal and Child Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

^b Key Laboratory of Environment and Health, Ministry of Education, and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

^c Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430015, China

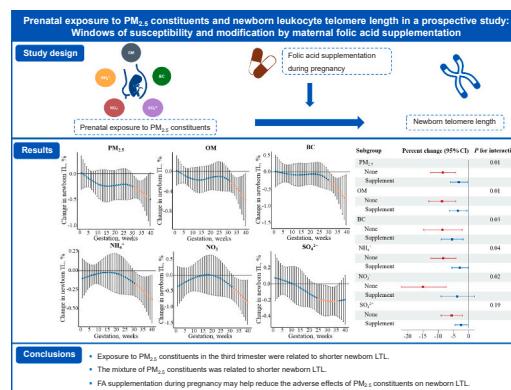
^d School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

^e Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD 20740, USA

HIGHLIGHTS

- PM_{2.5} constituents in the third trimester were related to shorter newborn LTL.
- The most sensitive window was identified at gestational weeks 31–40.
- The mixture of PM_{2.5} constituents was related to shorter newborn LTL.
- FA supplementation helps reduce the effects of PM_{2.5} constituents on newborn LTL.

GRAPHICAL ABSTRACT



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ABSTRACT

Prenatal exposure to fine particulate matter (PM_{2.5}) is related to alterations in newborn telomere length (TL), an indicator of cellular aging. However, the specific effects of PM_{2.5} constituents and windows of susceptibility are

* Corresponding author.

** Correspondence to: School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Hangkong Road 13, Wuhan, Hubei 430030, China.

E-mail addresses: xiaoninglei@sjtu.edu.cn (X. Lei), song_lulu@hust.edu.cn (L. Song).

¹ ORCID: 0000-0002-9105-2580

Newborn
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Telomere length

unknown. We aimed to identify the susceptibility windows for prenatal PM_{2.5} constituents affecting newborn leukocyte TL (LTL) and examine the modifying role of folic acid (FA) supplementation. This study involved 741 maternal-infant dyads from a birth cohort in Wuhan, China. We applied multiple linear regression, distributed lag models, and three multi-pollutant approaches to explore the effects of PM_{2.5} constituents on newborn LTL. Prenatal PM_{2.5} constituent exposures were related to shorter newborn LTL. Each 5 µg/m³ increase in organic matter (OM) and nitrate (NO₃⁻), and each 1 µg/m³ increase in black carbon (BC), ammonium (NH₄⁺), and sulfate (SO₄²⁻) during the third trimester were related to reductions in LTL of 3.99% (95% confidence interval [CI]: -6.36%, -1.56%), 6.31% (95% CI: -10.67%, -1.73%), 6.63% (95% CI: -9.87%, -3.27%), 3.69% (95% CI: -5.99%, -1.34%), and 3.00% (95% CI: -5.03%, -0.92%), respectively. The mixture of PM_{2.5} constituents was related to shorter newborn LTL, predominantly driven by OM and BC. The detrimental effects of OM, BC, NH₄⁺, and NO₃⁻ on newborn LTL were more pronounced in individuals without FA supplementation (all *P* for interaction < 0.05). Our findings identify the third trimester as a susceptibility window for PM_{2.5} constituent-induced LTL shortening, with OM and BC as the primary contributors. FA supplementation may help mitigate these effects, highlighting its potential as an intervention strategy.

1. Introduction

Telomeres, repetitive DNA sequences at chromosome ends, serve an essential role in maintaining chromosomal integrity and stability [1]. Telomere length (TL) is an important biomarker of cellular aging, progressively shortening with cell division [2]. Research has revealed that individuals with shorter TL are more likely to develop age-related diseases, such as cardiovascular disease [3], diabetes [4], and cancer [5]. Although most studies on TL focus on adults, newborn TL represents the initial setting and holds significant influence on telomere dynamics throughout life [6,7]. A decrease in the initial TL may act as a potential biomarker, offering insights into determinants of lifetime health [8]. Thus, identifying determinants that affect newborn TL could provide insights into the fetal origins of adult diseases.

Particulate matter, particularly fine particulate matter (PM_{2.5}), has been identified as a potential environmental factor influencing TL [9]. Evidence indicates that exposure to PM_{2.5} can induce oxidative stress and inflammation [10]. Oxidative stress leads to the production of reactive oxygen species (ROS), which can directly damage telomeres due to their high guanine content [11]. This damage results in the accumulation of single-strand breaks, thereby accelerating telomere shortening [12]. Additionally, increased inflammatory activity can further accelerate telomere shortening by promoting heightened cell turnover [13]. Epidemiological studies have suggested that prenatal exposure to PM_{2.5} is related to shorter newborn TL [14–17], though some findings remain inconsistent [18,19], and critical windows of susceptibility remain uncertain. PM_{2.5} is a mixture of chemical constituents, such as organic matter (OM), black carbon (BC), ammonium (NH₄⁺), nitrate (NO₃⁻), and sulfate (SO₄²⁻), with toxicity largely determined by these constituents [20,21]. Until now, only one birth cohort study in Denmark has assessed the impacts of prenatal BC and NH₄⁺ exposures on newborn TL [19]. However, this study was carried out in a developed country with relatively low exposure levels and did not account for high collinearity among these constituents. Additionally, the relationships of other PM_{2.5} constituents like OM, NO₃⁻, and SO₄²⁻ during pregnancy with newborn TL remain unexplored. Therefore, further research using multi-pollutant methods is essential to disentangle the impacts of different PM_{2.5} constituents on newborn TL, especially in highly polluted regions like China.

Emerging evidence suggests that folic acid (FA) supplementation during pregnancy plays a vital role in fetal growth and development [22, 23]. Research has indicated that prenatal FA supplementation is related to longer newborn TL [24,25]. Additionally, experimental research has shown that FA can mitigate damage by reducing oxidative stress-induced telomere attrition [26–28]. However, it has not yet been examined whether FA supplementation modifies the impacts of prenatal PM_{2.5} constituent exposures on newborn TL.

Therefore, using a birth cohort study, we aimed to: 1) evaluate the weekly and cumulative effects of PM_{2.5} constituents during pregnancy on newborn leukocyte telomere length (LTL) and identify sensitive

windows; 2) assess the joint effects of these constituents using multi-pollutant approaches; and 3) explore the modifying role of FA supplementation in the relationships between PM_{2.5} constituents and LTL.

2. Methods

2.1. Study population

This study utilized data from a birth cohort conducted at Wuhan Children's Hospital between November 2013 and March 2015. The cohort consists of pregnant women recruited during their first-trimester prenatal examinations after obtaining written informed consent. Longitudinal follow-up assessments were carried out at standardized intervals: during the second and third trimesters, at delivery, and during postpartum follow-ups at 1 month, 6 months, 1 year, 2 years, and beyond. To ensure data quality, all investigators completed standardized training covering recruitment protocols, data collection, and sample management procedures before initiating fieldwork. Trained investigators conducted standardized face-to-face interviews to ensure data accuracy. Trained nurses strictly followed standard operating procedures for biological sample collection, processing, and storage. Regular audits and continuous oversight were implemented to monitor compliance with standardized operating procedures and to ensure the authenticity and consistency of the questionnaire data. A total of 762 maternal-infant dyads were initially enrolled, meeting the following inclusion criteria: 1) maternal age ≥ 18 years; 2) residing in Wuhan City for ≥ 1 year prior to recruitment; 3) singleton pregnancy of < 16 weeks at recruitment; 4) planning to receive antenatal care and deliver at the study hospital; and 5) willing to provide biological samples, complete questionnaires, and participate in follow-up visits. After excluding 16 participants lacking cord blood samples or with low DNA quality and 5 participants with missing address information, the final analysis comprised 741 maternal-infant dyads. The study area is depicted in Fig. 1.

This study received ethical approval from the Ethics Committee of Wuhan Children's Hospital (No. 2016003) and Tongji Medical College, Huazhong University of Science and Technology (No. S152). All participants provided informed consent at enrollment.

2.2. Exposure assessment

Data on PM_{2.5} and its constituents, including OM, BC, NH₄⁺, NO₃⁻, and SO₄²⁻, were sourced at 1 × 1 km spatial resolution from the ChinaHigh-AirPollutants (CHAP) dataset (<https://weijing-rs.github.io/product.html>). The CHAP dataset was generated using a hybrid machine learning model as previously described [29]. The estimated levels of PM_{2.5} and its constituents have been effectively validated [29,30]. Daily exposure levels of PM_{2.5} and its constituents were extracted based on participants' residential addresses. Average concentrations for each gestational week were computed based on the daily concentrations. We then computed

the average concentrations of PM_{2.5} and its constituents for each trimester: the first trimester (weeks 1–13), the second trimester (weeks 14–26), and the third trimester (weeks 27–delivery). The average ambient temperature throughout pregnancy was calculated using daily temperature data from the global AgERA5 reanalysis data product (<https://doi.org/10.24381/cds.6c68c9bb>). The PM₁₀ and O₃ concentrations were obtained from the CHAP dataset at a spatial resolution of 1 × 1 km, while SO₂, CO, and NO₂ concentrations were sourced from the CHAP dataset at a spatial resolution of 10 × 10 km, as detailed in previous studies [31–33].

2.3. Newborn leukocyte telomere length (LTL) measurement

Umbilical cord blood samples were immediately collected into EDTA tubes following delivery and stored at –80 °C after centrifugation. The DNA extraction was performed 2–3 years after sample collection. Genomic DNA was extracted from cord blood leukocytes using the Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI, USA). The purity and concentration of the DNA were measured using a NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific, USA). DNA samples with an A260/A280 ratio between 1.8 and 2.0 were considered eligible. LTL in cord blood was determined using the ratio of telomere repeat copy number to single-copy gene number (T/S ratio) through quantitative polymerase chain reaction. A standard curve was generated from 50 randomly selected DNA samples covering a concentration range of 104–0.4 ng/μL ($R^2 \geq 0.99$). The coefficients of variation for intra-run and inter-run LTL measurements were 3.0 % and 4.1 %, respectively. Further information on the methods for measuring LTL is available in previous publication [34].

2.4. Maternal FA supplementation and covariates

Data on sociodemographic and lifestyle factors, including education, family income, maternal age, alcohol use during pregnancy, smoking during pregnancy, passive smoking, and FA supplementation, were collected via questionnaire. We gathered data on FA supplementation by

inquiring whether pregnant women took FA supplements during their pregnancy (none, supplement). As the guideline of the Nationwide Folic Acid Supplementation Program in China, it is recommended that pregnant women consume FA supplements at a daily dose of 400 μg [35]. Educational levels were classified into three groups: junior school or below, high school, and college or above. Family income was categorized into three groups: < 50,000, 50,000–100,000, and ≥ 100,000 yuan/year. Information on hypertensive disorders in pregnancy (HDP), gestational diabetes mellitus (GDM), parity, infant birth date, and infant sex was extracted from clinical records. Pre-pregnancy weight was self-reported, enabling the calculation of body mass index (BMI).

2.5. Statistical analysis

The correlations among PM_{2.5} and its constituents during pregnancy were estimated using spearman correlation coefficients. Due to its skewed distribution, LTL was log-transformed for the analysis. Distributed lag models (DLMs) were applied to estimate the relationships of weekly PM_{2.5} constituent exposures during pregnancy with newborn LTL, as well as to identify windows of susceptibility [36]. In DLMs, a cross-basis matrix was constructed to simultaneously account for exposure-response and lag-response dimensions [37]. The exposure-response dimension was assumed to be linear, and the lag-response dimension was fitted using natural cubic splines. Degrees of freedom for the lag-response dimension were set to 4 for PM_{2.5}, OM, BC, and SO₄²⁻, and 3 for NH₄⁺ and NO₃⁻, based on the Akaike information criterion and model performance. The lag range was set to 40 weeks, and for those delivering before 40 weeks of gestation, exposure was assigned zero in the weeks after delivery. We also utilized the DLMs to estimate the cumulative impacts of PM_{2.5} and its constituents on newborn LTL across the three trimesters and throughout pregnancy, as the majority of prior studies. Additionally, we employed traditional linear regression models to estimate the impacts of average exposures to PM_{2.5} and its constituents during each trimester and throughout pregnancy (actual pregnancy duration) on newborn LTL, referred to as “average exposure models”. To explore potential non-linear exposure-response

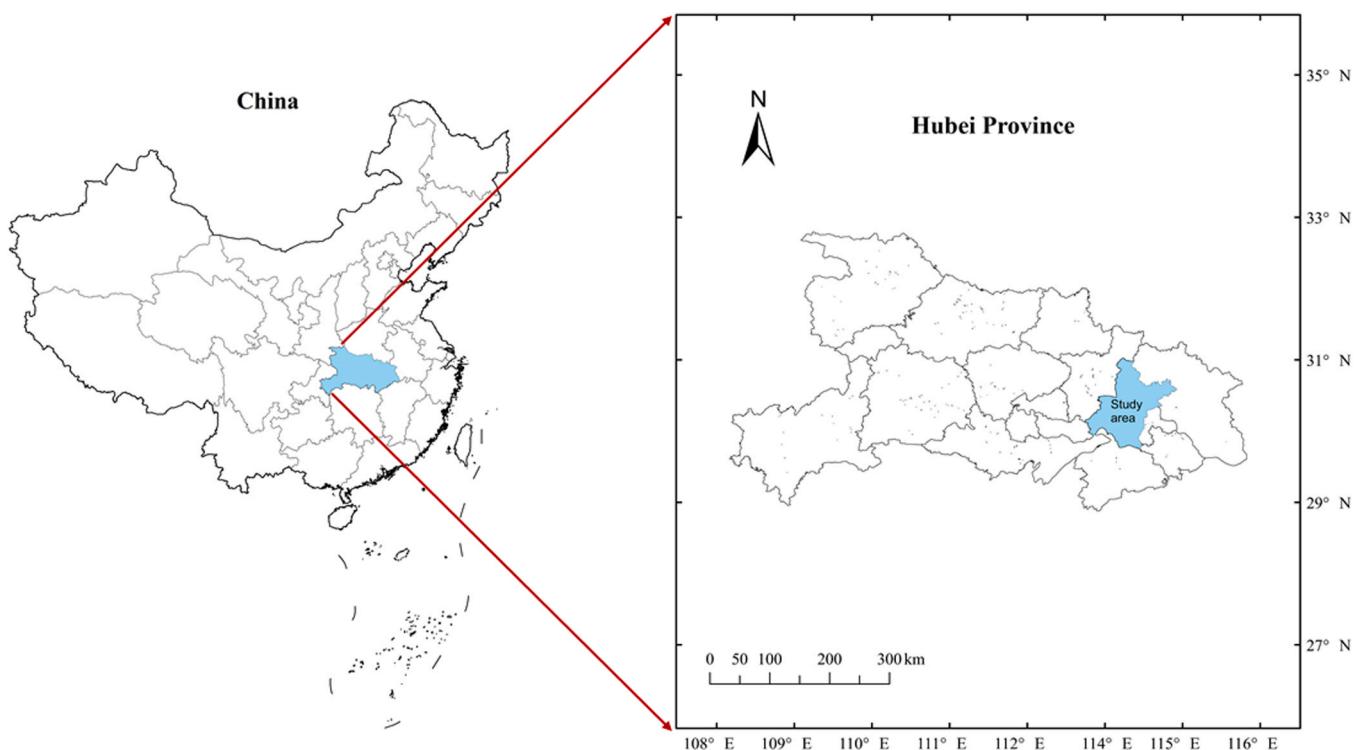


Fig. 1. Location of the study area.

relationships of PM_{2.5} and its constituents with newborn LTL, we applied restricted cubic spline regression models with three knots, selected based on minimization of the Akaike Information Criterion. The knots were placed at the 10th, 50th, and 90th percentiles of PM_{2.5} and its constituents, with the 10th percentile serving as the reference. All models were adjusted for educational level, family income, maternal age, passive smoking during pregnancy, pre-pregnancy BMI, GDM, HDP, FA supplementation, parity, infant sex, season at delivery, and ambient temperature. Smoking and alcohol use during pregnancy were not included in the models because no instances were reported. To facilitate interpretation, the results were presented as percent change (95 % confidence interval [CI]) in LTL for each 10 µg/m³ increase in PM_{2.5}, 5 µg/m³ increase in OM and NO₃⁻, and 1 µg/m³ increase in BC, NH₄⁺, and SO₄²⁻.

To explore the joint impacts of PM_{2.5} constituents on newborn LTL, we employed three multi-pollutant approaches: Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS), and quantile g-computation (QGC). BKMR uses a kernel machine approach to estimate the overall mixture effect and calculate posterior inclusion probabilities, reflecting the importance of individual PM_{2.5} constituents. The WQS model computes the WQS index, which facilitates identifying the relative significance of PM_{2.5} constituents and their combined effects on newborn LTL. QGC is a flexible model that assesses the joint impact of raising all constituents in the mixture by quantile and assesses the weights of PM_{2.5} constituents, either positive or negative. Detailed descriptions of these methods are available in the [Supplementary Methods](#).

Subgroup analyses were conducted to estimate the modifying effects of FA supplementation on the relationships of prenatal exposures to PM_{2.5} and its constituents with newborn LTL. Interaction effects were evaluated by incorporating a product term into the models. For the DLM models, the product term was constructed using the cross-basis for PM_{2.5} constituents and FA supplementation. The significance of interaction effects was tested using the likelihood ratio test by comparing models with and without the interaction term. Besides, to explore the potential effect of other factors, we conducted subgroup analyses stratified by parity (primiparous/multiparous), maternal age (< 28 years/ ≥ 28 years, based on the median), and newborn birth weight (< 3300 g/ ≥ 3300 g, based on the median).

To test the robustness of the main results, several sensitivity analyses were performed: (1) limiting the exposure window to 0–36 weeks; (2) excluding preterm infants (gestational age < 37 weeks); (3) excluding women with GDM or HDP; and (4) further adjusting for other air pollution, including O₃, PM₁₀, SO₂, CO, and NO₂.

All statistical analyses were conducted using R (version 4.4.1) with the R packages “dlnm”, “gWQS”, “qgcomp”, and “bkmr”. A two-tailed *P* value < 0.05 was deemed statistically significant.

3. Results

3.1. Characteristics of participants

Table 1 shows the characteristics of the participants. The average maternal age was 28.6 ± 3.3 years. Among the 741 women, 576 (77.7 %) took FA supplements during pregnancy. The median (25th, 75th percentiles) newborn LTL was 0.74 (0.56, 0.95). [Figure S1](#) presents the levels of PM_{2.5} and its constituents during pregnancy. The median (IQR) levels of PM_{2.5}, OM, BC, NH₄⁺, NO₃⁻, and SO₄²⁻ during the entire pregnancy were 75.91 (7.93), 29.43 (3.97), 6.05 (0.56), 8.69 (0.80), 15.06 (2.51), and 14.44 (1.13) µg/m³, respectively. Spearman correlations coefficients among PM_{2.5} and its constituents ranged from 0.27 to 0.99 ([Figure S2](#)).

3.2. Associations of prenatal PM_{2.5} and its constituents with newborn LTL

[Fig. 2](#) displays the weekly relationships of PM_{2.5} and its constituents with newborn LTL, as assessed by DLMs. Weekly exposures to PM_{2.5} and

Table 1
Characteristics of 741 mother-newborn pairs.

Variables	Number (%)	Leukocyte telomere length	P value
Total	741	0.74 (0.56, 0.95)	
Maternal age (years)			0.08
< 35	693 (93.5)	0.73 (0.56, 0.95)	
≥ 35	48 (6.5)	0.81 (0.69, 0.91)	
Pre-pregnancy BMI (kg/m ²)			0.23
< 18.5	138 (18.6)	0.77 (0.58, 0.97)	
18.5–23.9	507 (68.4)	0.72 (0.55, 0.94)	
≥ 24	96 (13.0)	0.76 (0.63, 0.91)	
Education level			0.32
Junior school or below	42 (5.7)	0.70 (0.52, 0.85)	
High school	114 (15.4)	0.77 (0.56, 0.99)	
College or above	585 (78.9)	0.74 (0.56, 0.95)	
Family income (yuan/year)			0.04
< 50,000	145 (19.6)	0.74 (0.55, 0.99)	
50,000–100,000	287 (38.7)	0.72 (0.55, 0.89)	
≥ 100,000	309 (41.7)	0.78 (0.59, 0.97)	
Passive smoking during pregnancy			< 0.001
Yes	243 (32.8)	0.69 (0.53, 0.88)	
No	498 (67.2)	0.77 (0.58, 0.99)	
Folic acid supplementation			< 0.001
Yes	576 (77.7)	0.77 (0.58, 0.97)	
No	165 (22.3)	0.64 (0.51, 0.85)	
Parity			0.22
Primiparous	640 (86.4)	0.73 (0.56, 0.95)	
Multiparous	101 (13.6)	0.78 (0.61, 0.91)	
Gestational diabetes mellitus			0.80
Yes	53 (7.2)	0.76 (0.65, 0.89)	
No	688 (92.8)	0.74 (0.56, 0.95)	
Hypertensive disorders in pregnancy			0.03
Yes	19 (2.6)	0.55 (0.51, 0.76)	
No	722 (97.4)	0.74 (0.56, 0.95)	
Gestational age (week)			0.88
< 37	18 (2.4)	0.70 (0.61, 0.95)	
≥ 37	723 (97.6)	0.74 (0.56, 0.95)	
Season at delivery			< 0.001
Spring (March–May)	205 (27.7)	0.66 (0.54, 0.87)	
Summer (June–August)	261 (35.2)	0.78 (0.61, 0.96)	
Autumn (September–November)	130 (17.5)	0.77 (0.55, 1.05)	
Winter (December–February)	145 (19.6)	0.74 (0.55, 0.97)	
Infant sex			0.95
Male	382 (51.6)	0.74 (0.56, 0.97)	
Female	359 (48.4)	0.74 (0.55, 0.93)	
Newborn birth weight (g)			0.11
< 2500	15 (2.0)	0.64 (0.61, 0.74)	
2500–4000	688 (92.9)	0.75 (0.56, 0.96)	
> 4000	38 (5.1)	0.68 (0.52, 0.81)	

Newborn leukocyte telomere length is reported as the median (25th, 75th percentiles). *P* values were calculated using the Mann-Whitney *U* test or Kruskal-Wallis test to compare telomere length across different characteristic categories.

its constituents were linked to shorter newborn LTL. The critical exposure windows for each constituent were identified as follows: PM_{2.5} during gestational weeks 31–39; OM during weeks 32–40; BC during weeks 31–40; NH₄⁺ during weeks 31–40; NO₃⁻ during weeks 32–40; and SO₄²⁻ during weeks 25–36.

Table 2 presents the impacts of PM_{2.5} and its constituents on newborn LTL during each trimester and the entire pregnancy period, using both DLMs and linear regression models. PM_{2.5} and its constituents over the entire pregnancy were negatively related to newborn LTL, showing percent changes of -6.71 % (95 % CI: -11.53 %, -1.62 %) for PM_{2.5} (per 10 µg/m³ increase), -5.32 % (95 % CI: -9.65 %, -0.78 %) for OM (per 5 µg/m³ increase), -7.15 % (95 % CI: -11.80 %, -2.25 %) for BC (per 1 µg/m³ increase), -4.17 % (95 % CI: -8.17 %, -0.01 %) for NH₄⁺ (per 1 µg/m³ increase), and -3.26 % (95 % CI: -6.26 %, -0.17 %) for SO₄²⁻ (per 1 µg/m³ increase). An increase of 10 µg/m³ in

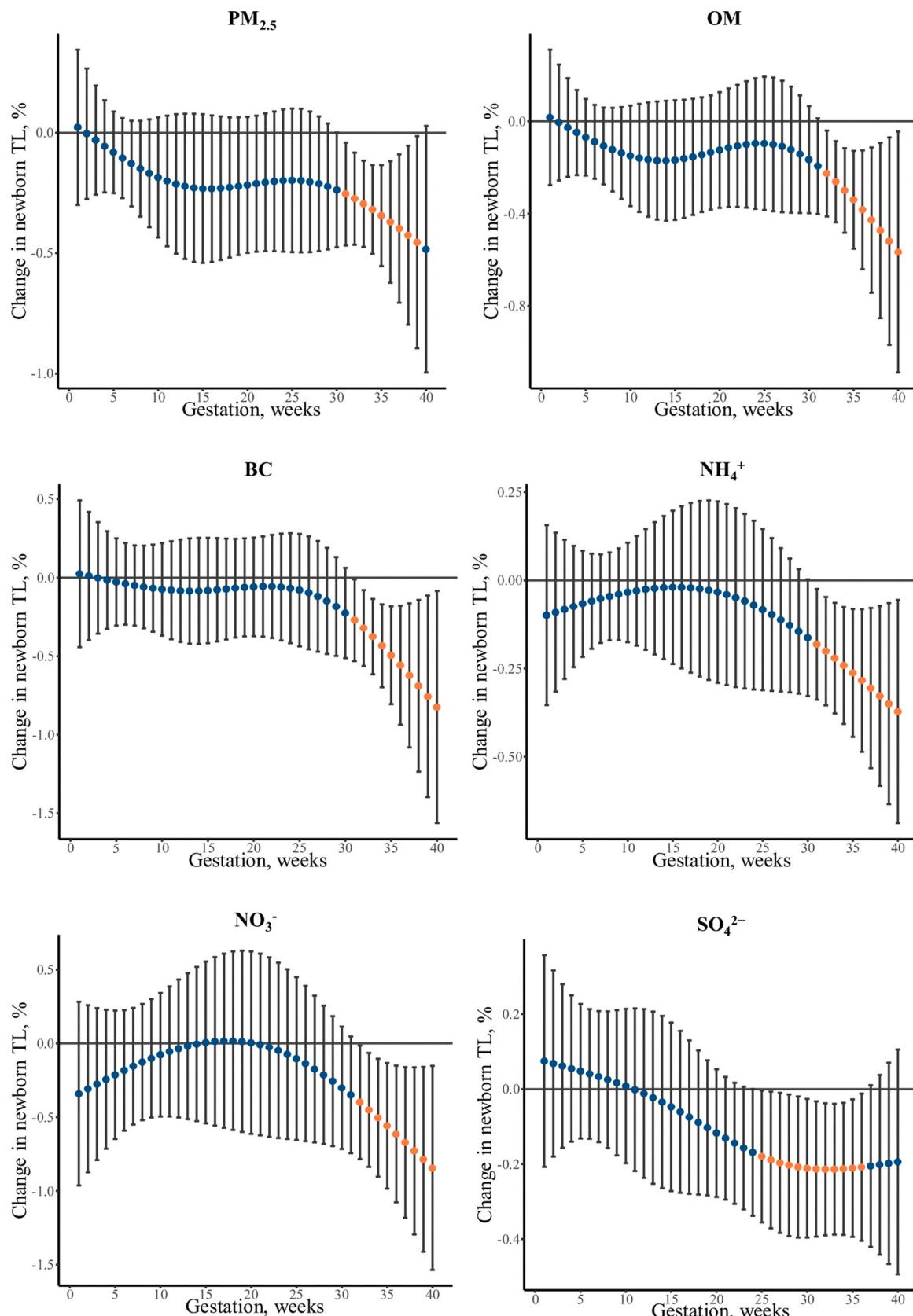


Fig. 2. Associations between weekly exposure to PM_{2.5} constituents during pregnancy and newborn leukocyte telomere length (n = 741). Week-specific estimates provided as a percentage change in TL (95 % CI) for a 10 µg/m³ increase in PM_{2.5}, 5 µg/m³ increase in OM, NO₃⁻, and 1 µg/m³ increase in BC, NH₄⁺, and SO₄²⁻. Model was adjusted for maternal age at delivery, pre-pregnancy BMI, educational level, family income, passive smoking during pregnancy, gestational diabetes mellitus, hypertensive disorders in pregnancy, folic acid supplementation, parity, infant sex, season at delivery, and ambient temperature.

Table 2Associations between exposure to PM_{2.5} constituents during pregnancy and newborn leukocyte telomere length (n = 741).

	Distributed lag model		Average exposure model	
	Crude model	Adjusted model	Crude model	Adjusted model
First trimester				
PM _{2.5}	2.20 (0.96, 3.47)	0.76 (-1.08, 2.64)	2.20 (0.95, 3.47)	0.06 (-1.79, 1.95)
OM	2.14 (0.86, 3.43)	0.54 (-1.24, 2.36)	2.16 (0.89, 3.45)	0.01 (-1.79, 1.85)
BC	2.32 (-0.03, 4.72)	-0.35 (-3.35, 2.76)	2.94 (0.56, 5.38)	-1.21 (-4.23, 1.91)
NH ₄ ⁺	1.74 (0.58, 2.90)	-0.09 (-1.71, 1.56)	1.85 (0.73, 2.99)	-0.08 (-1.72, 1.60)
NO ₃ ⁻	3.79 (1.37, 6.27)	1.54 (-2.59, 5.85)	4.75 (2.38, 7.17)	1.44 (-2.72, 5.78)
SO ₄ ²⁻	0.70 (-0.69, 2.12)	-0.28 (-1.95, 1.41)	0.57 (-0.87, 2.03)	-0.65 (-2.33, 1.06)
Second trimester				
PM _{2.5}	-0.73 (-2.54, 1.11)	-0.71 (-4.67, 3.42)	-0.58 (-2.18, 1.04)	-1.13 (-4.41, 2.25)
OM	-0.79 (-2.65, 1.11)	-0.83 (-4.45, 2.93)	-0.61 (-2.23, 1.04)	-1.19 (-4.21, 1.91)
BC	-4.20 (-7.05, -1.26)	-3.25 (-7.38, 1.07)	-3.45 (-6.06, -0.76)	-2.53 (-6.24, 1.33)
NH ₄ ⁺	-0.75 (-2.46, 0.99)	-0.44 (-4.20, 3.47)	-0.56 (-2.12, 1.03)	-0.58 (-3.98, 2.94)
NO ₃ ⁻	-1.05 (-4.12, 2.12)	1.57 (-7.52, 11.55)	-0.87 (-3.51, 1.83)	0.26 (-7.61, 8.79)
SO ₄ ²⁻	1.88 (-0.37, 4.17)	-0.26 (-2.65, 2.18)	1.32 (-0.55, 3.24)	-0.65 (-2.74, 1.49)
Third trimester				
PM _{2.5}	-3.93 (-5.29, -2.54)	-4.74 (-7.05, -2.38)	-3.49 (-4.81, -2.14)	-4.04 (-6.37, -1.65)
OM	-4.32 (-5.83, -2.78)	-5.14 (-7.56, -2.66)	-3.73 (-5.17, -2.26)	-3.99 (-6.36, -1.56)
BC	-5.64 (-7.71, -3.52)	-6.33 (-9.38, -3.18)	-5.23 (-7.33, -3.08)	-6.63 (-9.87, -3.27)
NH ₄ ⁺	-3.70 (-4.97, -2.41)	-4.30 (-6.56, -1.99)	-3.22 (-4.47, -1.95)	-3.69 (-5.99, -1.34)
NO ₃ ⁻	-6.63 (-9.03, -4.18)	-7.14 (-11.52, -2.55)	-5.55 (-7.75, -3.31)	-6.31 (-10.67, -1.73)
SO ₄ ²⁻	-3.46 (-4.98, -1.92)	-3.05 (-4.84, -1.22)	-3.86 (-5.51, -2.19)	-3.00 (-5.03, -0.92)
Entire pregnancy				
PM _{2.5}	-5.92 (-10.24, -1.39)	-7.50 (-13.01, -1.65)	-4.34 (-8.60, 0.13)	-6.71 (-11.53, -1.62)
OM	-5.27 (-9.35, -1.01)	-6.29 (-11.01, -1.32)	-2.88 (-6.87, 1.28)	-5.32 (-9.65, -0.78)
BC	-6.97 (-11.51, -2.20)	-6.56 (-11.40, -1.47)	-8.00 (-12.48, -3.30)	-7.15 (-11.80, -2.25)
NH ₄ ⁺	-4.93 (-8.54, -1.17)	-4.06 (-8.58, -0.70)	-3.06 (-6.70, -0.72)	-4.17 (-8.17, -0.01)
NO ₃ ⁻	-10.58 (-19.95, 0.12)	-8.43 (-20.67, 5.70)	-5.99 (-13.45, 2.12)	-11.61 (-23.10, 1.60)
SO ₄ ²⁻	-2.45 (-5.85, 1.06)	-3.66 (-7.13, -0.06)	-1.75 (-4.56, 1.15)	-3.26 (-6.26, -0.17)

Model was adjusted for maternal age at delivery, pre-pregnancy BMI, educational level, family income, passive smoking during pregnancy, gestational diabetes mellitus, hypertensive disorders in pregnancy, folic acid supplementation, parity, infant sex, season at delivery, and ambient temperature.

Units are a 10 µg/m³ increase in PM_{2.5}, 5 µg/m³ increase in OM, NO₃⁻, and 1 µg/m³ increase in BC, NH₄⁺, and SO₄²⁻.

PM_{2.5}, 5 µg/m³ in OM and NO₃⁻, and 1 µg/m³ in BC, NH₄⁺, and SO₄²⁻ during the third trimester were related to reductions in newborn LTL of 4.04 % (95 % CI: -6.37 %, -1.65 %), 3.99 % (95 % CI: -6.36 %, -1.56 %), 6.31 % (95 % CI: -10.67 %, -1.73 %), 6.63 % (95 % CI: -9.87 %, -3.27 %), 3.69 % (95 % CI: -5.99 %, -1.34 %), and 3.00 % (95 % CI: -5.03 %, -0.92 %), respectively. No significant relationships were identified of PM_{2.5} and its constituents with newborn LTL during the first and second trimesters. The estimates from the DLMs aligned with those from the average exposure models. Restricted cubic spline analyses indicated linear inverse relationships of PM_{2.5} and its constituents with newborn LTL (Fig. 3A, all P for nonlinear > 0.05).

3.3. Joint effect of PM_{2.5} constituents on newborn LTL

We further examined the joint effect of the mixture of PM_{2.5} constituents during the third trimester on newborn LTL. WQS and QGC models indicated an inverse relationship between the mixture of PM_{2.5} constituents and newborn LTL, showing a percent change in LTL of -8.63 % (95 % CI: -15.46 %, -0.48 %) and -6.29 % (95 % CI: -10.92 %, -1.41 %) per quartile increase in the mixture, respectively. Similar results were observed in the BKMR analysis (Fig. 3C). OM and BC were consistently identified as the primary contributors to the reduction in newborn LTL associated with exposure to the PM_{2.5} constituent mixture (Fig. 3B).

3.4. Effect modification by maternal folic acid supplementation

Fig. 4 and Table S1 illustrate the modifying effects of maternal FA supplementation on the relationships between PM_{2.5} and its constituents in the third trimester and newborn LTL. The relationships of PM_{2.5} and its constituents with newborn LTL were more pronounced in individuals without FA supplementation, showing percent changes in average exposure models of PM_{2.5} (-8.44 %, 95 % CI: -12.90 %, -3.74 %), OM

(-8.71 %, 95 % CI: -13.33 %, -3.84 %), BC (-9.08 %, 95 % CI: -15.95 %, -1.65 %), NH₄⁺ (-8.60 %, 95 % CI: -13.02 %, -3.97 %), NO₃⁻ (-15.06 %, 95 % CI: -22.68 %, -6.70 %), and SO₄²⁻ (-5.90 %, 95 % CI: -10.25 %, -1.34 %). Significant interaction effects were observed between FA supplementation and PM_{2.5}, OM, BC, NH₄⁺, and NO₃⁻ exposure on newborn LTL (all P for interaction < 0.05).

3.5. Subgroup analyses and sensitivity analyses

Subgroup analyses show no significant differences across parity (primiparous/multiparous), maternal age (< 28 years/≥ 28 years), and newborn birth weight (< 3300 g/≥ 3300 g) (Tables S2-S4, all P for interaction > 0.05). Limiting the exposure window to 0–36 weeks, the associations of exposure to PM_{2.5} constituents during the third trimester and the entire pregnancy with LTL remained robust (Table S5). Besides, the negative relationships of PM_{2.5} and its constituents with newborn LTL remained unchanged after excluding preterm infants or excluding women with GDM and HDP (Table S6 and Table S7). After further adjusting for O₃, PM₁₀, SO₂, CO, and NO₂, the results were consistent with the main findings (Table S8).

4. Discussion

In this birth cohort study, we observed that prenatal PM_{2.5} constituent exposures was related to shorter newborn LTL, with the third trimester identified as a vulnerable period. The mixture of PM_{2.5} constituents during the third trimester has negative effects on newborn LTL, with OM and BC being key contributors. Furthermore, FA supplementation was found to mitigate the harmful impacts of PM_{2.5} constituents on newborn LTL.

Several studies have indicated a relationship of prenatal PM_{2.5} exposure with shorter newborn TL [14–17], although these findings are not consistent [18,19]. These differing results may be influenced by the

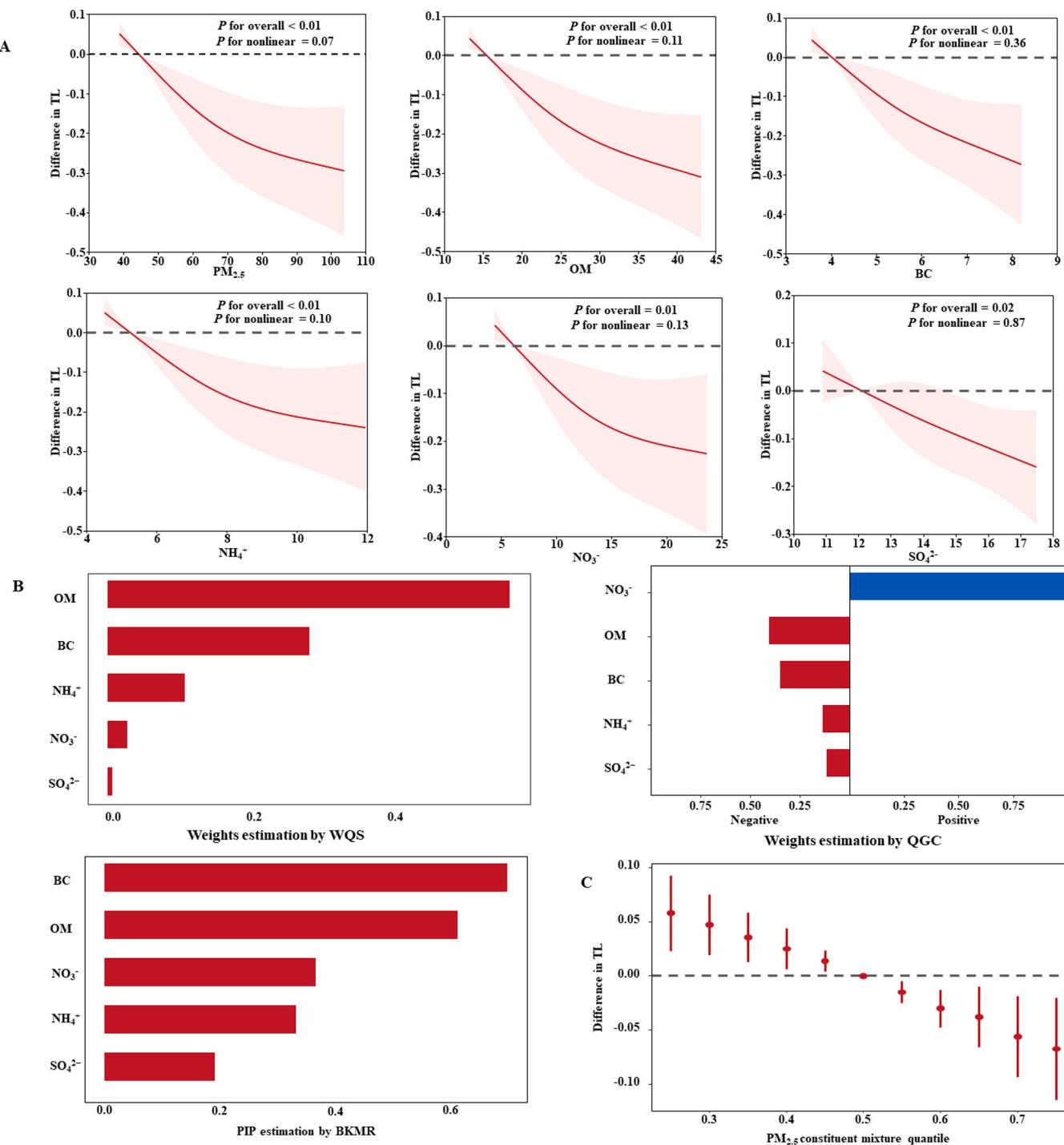


Fig. 3. Associations of exposure to PM_{2.5} constituents during the third trimester and newborn leukocyte telomere length (n = 741). (A) Dose-response relationships for individual PM_{2.5} constituents and newborn leukocyte telomere length, analyzed using restricted cubic spline regression models (knots at 10th, 50th, and 90th percentiles; reference=10th percentile). (B) Relative importance estimation of PM_{2.5} constituents in the mixture, with constituent weights derived from weighted quantile sum (WQS) and quantile g-computation (QGC) analyses, and posterior inclusion probabilities from Bayesian kernel machine regression (BKMR). Higher values indicate greater importance. (C) Overall mixture effects of PM_{2.5} constituents on newborn leukocyte telomere length.

toxicity of varying PM_{2.5} constituent concentrations. Nevertheless, research on associations of PM_{2.5} constituents with TL remains limited. For example, one study conducted among 165 American elderly men reported that annual BC exposure was associated with shorter TL [38]. Similarly, another study involving 197 Belgian children reported a negative relationship between BC exposure over the past week and TL [39]. Newborn TL holds significant implications for further health [6,7]. To date, only one study involving 296 mother-child pairs has evaluated

the relationship of newborn TL with prenatal exposure to BC and NH₄⁺ at low exposure levels. This study indicated that second-trimester BC exposure was linked to longer newborn TL, while third-trimester exposures to BC and NH₄⁺ exposure were linked to shorter newborn TL [19]. The average concentrations of NH₄⁺ and BC in our study exceeded those indicated in the previous research (NH₄⁺: 8.7 µg/m³ vs. 0.6 µg/m³; BC: 6.1 µg/m³ vs. 0.5 µg/m³). We also observed negative associations between third-trimester exposures to BC and NH₄⁺ and newborn LTL.

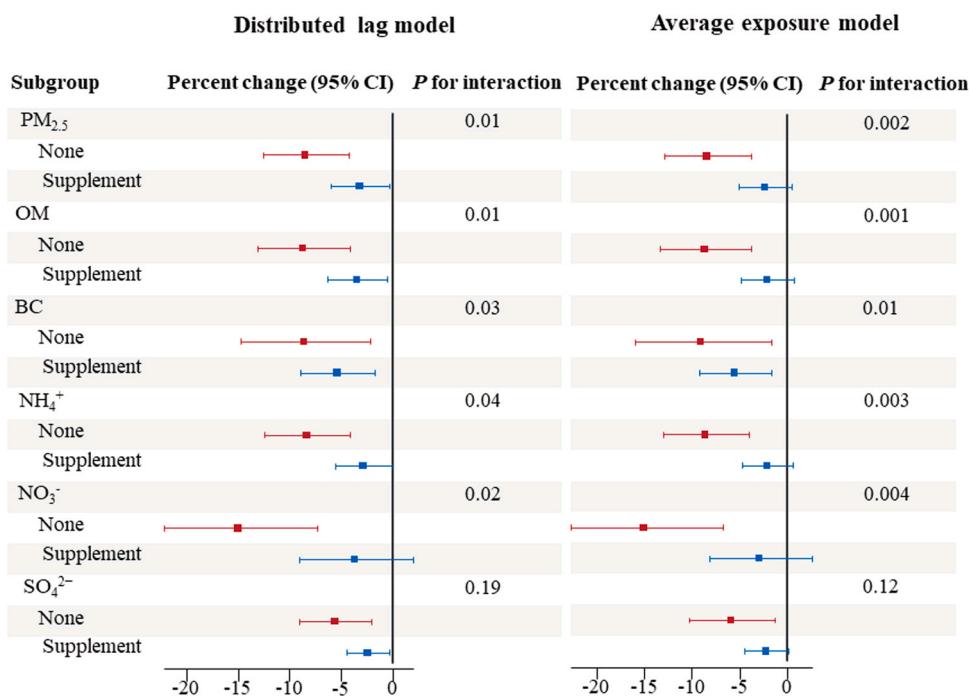


Fig. 4. Effect modification of folic acid supplementation on the associations between exposure to PM_{2.5} constituents during the third trimester of pregnancy and newborn leukocyte telomere length (n = 741). Model was adjusted for maternal age at delivery, pre-pregnancy BMI, educational level, family income, passive smoking during pregnancy, gestational diabetes mellitus, hypertensive disorders in pregnancy, parity, infant sex, season at delivery, and ambient temperature. Units are a 10 µg/m³ increase in PM_{2.5}, 5 µg/m³ increase in OM, NO₃⁻, and 1 µg/m³ increase in BC, NH₄⁺, and SO₄²⁻.

However, unlike the previous study, we identified no significant relationship of second-trimester BC exposure with newborn LTL. This discrepancy could be attributed to variations in exposure duration, exposure levels, assessment methods, and the populations being exposed. Furthermore, we examined the relationships of other PM_{2.5} constituents, including OM, NO₃⁻, and SO₄²⁻ with newborn LTL, which have not been explored in prior research.

Currently, no research has examined the joint effect of multiple PM_{2.5} constituents on newborn TL or identified the key contributors. We found that the mixture of PM_{2.5} constituents negatively affects newborn LTL, with BC and OM being the primary causes. BC and OM primarily result from the insufficient burning of organic matter and fossil fuels, including traffic exhaust and agricultural burning [40], while NH₄⁺, NO₃⁻, and SO₄²⁻ are primarily formed through the transformation of pollutants originating from industrial coal burning, power plants, and vehicle emissions [41,42]. Therefore, our findings suggest that targeted control strategies aimed at reducing BC and OM, key primary air pollutants, may be more effective in mitigating the harmful influence of PM_{2.5} on newborn LTL.

The exact mechanisms by which prenatal PM_{2.5} constituents influence newborn LTL remain unclear, but one possible explanation is their ability to trigger oxidative stress and inflammation [43,44], both of which have been linked to shorter LTL [12,45]. Specifically, PM_{2.5} constituents generate ROS [46], which can induce DNA damage, leading to strand breaks and subsequently accelerating telomere shortening during cellular replication [11]. Additionally, oxidative stress can activate DNA repair enzymes, which may unintentionally speed up telomere shortening through processes like non-homologous end joining or alternative lengthening of telomeres [47]. The chemical properties of PM_{2.5} constituents may also play a critical role in altering LTL. Our findings indicate that BC and OM are the primary contributors to the effect of PM_{2.5} constituents on newborn LTL. Evidence suggests that particles from incomplete combustion, such as BC and OM, are more toxicologically potent than those emitted from more complete combustion processes [48–50]. These constituents can penetrate the

placenta and accumulate on the fetal side, thereby exacerbating their harmful effects on fetal development and potentially contributing to telomere shortening [49,51].

Our study identified the third trimester as a vulnerable period for the associations of PM_{2.5} and its constituents with newborn LTL. During this stage, fetal growth and development accelerate more rapidly than in the first and second trimesters, which may increase fetus susceptibility to PM_{2.5} constituent exposure due to increased cell division [52]. Furthermore, this vulnerable window coincides with the developmental changes in the placental barrier and maternal-fetal circulation. During the third trimester, the placenta exhibits a reduction in the number of cell layers separating maternal and fetal blood circulations, resulting in a thinner barrier [53,54]. This change may facilitate the transfer of PM_{2.5} constituents into the fetal circulation, potentially causing oxidative stress and inflammation, resulting in shortened telomeres [55].

This study revealed that FA supplementation attenuated the harmful effects of PM_{2.5} constituents on newborn LTL. Although the role of FA supplementation on the relationships of PM_{2.5} constituents with newborn LTL has not been investigated, previous studies have indicated that FA supplementation may lower the risks of macrosomia and preterm birth related to prenatal PM_{2.5} exposure [56,57]. As a B-vitamin, FA functions as a crucial coenzyme and methyl donor, playing a key role in DNA methylation [58]. Maternal FA supports fetal DNA integrity and methylation and has antioxidant properties [59,60], all of which impact newborn LTL [11,61]. Experimental studies have demonstrated that FA can counteract telomere attrition caused by oxidative stress [26–28]. Therefore, FA supplementation may help reduce the impacts of PM_{2.5} constituents on telomere shortening by reducing oxidative stress. This finding underscores the importance of FA supplementation in protecting against the harmful impacts of PM_{2.5} constituents on newborn health.

The present study has several strengths. It represents the first investigation into explore the impacts of multiple PM_{2.5} constituents on newborn LTL in a relatively large birth cohort. Additionally, we conducted a novel exploration of the association of PM_{2.5} constituent mixture with newborn LTL and estimated the contribution of each

constituent using three multi-pollutant methods. Using DLMs, we also performed a detailed analysis of weekly exposure levels during pregnancy to identify windows of susceptibility. Furthermore, we are the first to estimate the role of FA supplementation on the relationships of PM_{2.5} constituents with newborn LTL, which could have significant implications for intervention strategies. However, there are several limitations to be noted. First, data on indoor air pollution exposure was not collected, which may lead to exposure misclassification. Second, this study did not account for potential migration of study participants during pregnancy, which may influence their exposure level. Third, our exposure assessment focused on residential addresses and did not capture workplace exposures or time-activity patterns, potentially introducing exposure misclassification. Fourth, information on the specific dosage of FA supplementation was not gathered. Nevertheless, pregnant women typically consume FA supplements at a daily dosage of 400 µg, according to the guidelines of the Nationwide Folic Acid Supplementation Program in China [35]. Fifth, since all participants in this study were from China, caution is needed when generalizing our findings to other populations. Finally, despite efforts to account for various confounding variables, other factors that may influence newborn LTL, such as cell count and cell type, were not measured.

5. Conclusion

Our findings indicate that prenatal PM_{2.5} constituent exposures, including OM, BC, NH₄⁺, NO₃⁻, and SO₄²⁻, are associated with shorter newborn LTL, with the third trimester identified as the sensitive period. We also observed that the mixture of PM_{2.5} constituents had a negative impact on newborn LTL, with OM and BC being the primary contributors. Furthermore, our results suggest that FA supplementation can counteract these harmful effects. These findings highlight that reducing specific PM_{2.5} constituents, particularly OM and BC, could promote offspring health, and FA supplementation may serve as an effective intervention.

Environmental implication

Fine particulate matter (PM_{2.5}) presents a significant public health challenge due to its developmental toxicity, driven by its chemical components. However, the impact of prenatal exposure to PM_{2.5} constituents on newborn telomere length, a well-established biomarker of cellular aging, remains unclear. In this birth cohort study, we first found that exposure to PM_{2.5} constituents during the third trimester was associated with shorter newborn telomere length, with organic matter and black carbon being the primary contributors. Additionally, folic acid supplementation during pregnancy may help reduce these harmful effects.

Ethics approval

This study was approved by the ethics committees of Tongji Medical College, Huazhong University of Science and Technology (No. S152) and the Wuhan Children's Hospital (No. 2016003).

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CRediT authorship contribution statement

Fei Luo: Visualization, Investigation. **Jing Wei:** Methodology, Data curation. **Qing Fang:** Validation, Investigation. **Zitong Chen:**

Methodology, Data curation. **Xiaofeng Huang:** Visualization, Investigation. **Wenwen Guo:** Investigation. **Lulu Song:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Heng Li:** Investigation. **Xiaoning Lei:** Supervision, Methodology, Funding acquisition, Data curation. **Lianyan Yan:** Investigation. **Binghai Liu:** Investigation. **Chao Xiong:** Investigation. **Liqin Hu:** Investigation. **Xi Chen:** Supervision, Funding acquisition. **Qing Liu:** Validation, Investigation, Data curation. **Zhongqiang Cao:** Investigation. **Gaojie Fan:** Writing – original draft, Investigation, Formal analysis. **Youjie Wang:** 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.

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Informed consent

Informed consent was obtained from all participants included in the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2025.138747.

Data availability

Data will be made available on request.

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