Folic Acid Supplementation and the Association between Maternal Airborne Particulate Matter Exposure and Preterm Delivery: A National Birth Cohort Study in China

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BACKGROUND: Potential modification of the association between maternal particulate matter (PM) exposure and preterm delivery (PTD) by folic acid (FA) supplementation has not been studied.

OBJECTIVE: We examined whether FA supplementation could reduce the risk of PTD associated with maternal exposure to PM in ambient air during pregnancy.

METHOD: In a cohort study covering 30 of the 31 provinces of mainland China in 2014, 1,229,556 primiparas of Han ethnicity were followed until labor. We collected information on their FA supplementation and pregnancy outcomes and estimated each participant’s exposure to PM with diameters of ≤10 μm (PM10), 2.5 μm (PM2.5), and 1 μm (PM1) using satellite remote-sensing based models. Cox proportional hazard regression models were used to examine interactions between FA supplementation and PM exposures, after controlling for individual characteristics.

RESULTS: Participants who initiated FA ≥3 months prior to pregnancy (38.1%) had a 23% [hazard ratio (HR) = 0.77 (95% CI: 0.76, 0.78)] lower risk of PTD than women who did not use preconception FA. Participants with PM concentrations in the highest quartile had a higher risk of PTD [HR = 1.29 (95% CI: 1.26, 1.32) for PM10, 1.52 (95% CI: 1.46, 1.58) for PM2.5, and 1.22 (95% CI: 1.17, 1.27) for PM1] than those with exposures in the lowest PM quartiles. Estimated associations with a 10-μg/m3 increase in PM1, PM2.5 were significantly lower among women who initiated FA ≥3 months prior to pregnancy [HR = 1.09 (95% CI: 1.08, 1.10) for both exposures] than among women who did not use preconception FA [HR = 1.12 (95% CI: 1.11, 1.13) for both exposures; Pinteraction < 0.001]. The corresponding association was also significantly lower for a 10-μg/m3 increase in PM10 [HR = 1.03 (95% CI: 1.02, 1.03)] for FA ≥3 months before pregnancy vs. 1.04 (95% CI: 1.03, 1.04) for no preconception FA; Pinteraction < 0.001).

CONCLUSION: Our findings require confirmation in other populations, but they suggest that initiating FA supplementation ≥3 months prior to pregnancy may lessen the risk of PTD associated with PM exposure during pregnancy among primiparas of Han ethnicity. https://doi.org/10.1289/EHP6386

Introduction

According to the latest World Health Organization (WHO) report, preterm delivery (PTD) contributed to 35% of the 3.1 million neonatal deaths per year, acting as the leading cause of perinatal mortality in the world (March of Dimes et al. 2012). PTD may affect health throughout the life course by increasing the risk of neurodevelopmental disorders, learning impairment, visual disorders, and morbidity due to noncommunicable diseases, resulting in a heavy burden on families and society (March of Dimes et al. 2012). Therefore, numerous studies have tried to identify the causes of PTD and advance the development of preventive solutions (Shapiro-Mendoza et al. 2016).

During the last two decades, epidemiological studies, including research from our group, have reported that exposure to particulate matter (PM) with diameters of ≤1 μm (PM1), 2.5 μm (PM2.5), or 10 μm (PM10) in ambient air during pregnancy is associated with an increased risk of PTD (Li et al. 2018; Wang et al. 2018; Klepac et al. 2018; Yuan et al. 2019). Currently, a large proportion of pregnant women in China and other developing counties are exposed to PM concentrations above WHO air quality guidelines (van Donkelaar et al. 2015; WHO 2006). Therefore, there is an urgent need to reduce PM pollution and develop and implement interventions to protect pregnant women and their offspring from the adverse impacts of PM exposure.

Growing evidence shows that folic acid (FA) supplementation is important for the successful completion of fetal development (Jia et al. 2011; Zeisel 2009). Studies have also suggested that FA supplementation can reduce the risk of PTD (Bukowski et al. 2009; Li et al. 2014). As an essential B vitamin, FA is necessary in regulating DNA methylation processes and can act as a coenzyme or methyl donor in methyl group transfers, homocysteine synthesis, and redox states (Baccarelli et al. 2008; Stingone et al. 2017). Although potential mechanisms underlying associations between PM exposure and PTD are uncertain, epigenetic modifications,
including DNA methylation, have been proposed to link air pollution and adverse pregnancy outcomes (Stingone et al. 2017). However, to our knowledge, potential modification of the association between maternal PM exposure and PTD by FA supplementation has not been studied.

In the present cohort study, we aimed to examine whether initiating FA supplementation prior to pregnancy reduces the risk of PTD in association with maternal exposure to PM$_1$, PM$_2.5$, and PM$_{10}$ during pregnancy.

Methods

Study Population

Based on a previously described cohort of the National Free Preconception Health Examination Project (NFPHEP) (Li et al. 2018; Wang et al. 2018), we studied 1,535,545 women who had delivered babies from 1 December 2013 to 30 November 2014. Briefly, the Chinese National Health Commission and Ministry of Finance launched the NFPHEP to provide free health examinations and follow-up care through pregnancy for primiparas preparing for pregnancy in mainland China since 2010. Each woman’s demographic characteristics, lifestyle, pregnancy history, anthropometry, health conditions, last menstrual period (LMP), and pregnancy outcomes were prospectively examined and recorded in the program (Zhang et al. 2015). Of the 1,535,545 pregnancies, we excluded women whose exposure levels and pregnancy outcomes were not available (e.g., because of missing PM concentrations owing to continuously cloudy conditions or a missing gestational age, missing detailed home address, or change in residence); who were ethnic minority; <18 or >45 years of age at the time of delivery; who delivered at <20 wk or >42 wk gestational age or had multiple births; or who had diseases that may be associated with shorter gestational age (any self-reported history or diagnosis at the preconception examination of anemia, cancer, chronic nephritis, diabetes, lung disease, heart disease, hypertension, thyroid disorder, tuberculosis, or sexually transmitted disease) (Figure S1; Table S1). Finally, there were 1,229,566 primiparas of Han ethnicity included in the present study. The institutional review board of the National Research Institution for Family Planning, Beijing, China, approved the study, and all participants gave written informed consent.

Definition of PTD

Gestational age was estimated based on the first day of the LMP. The LMP was recorded at the early pregnancy visit (no later than 12 wk after conception) and the postpartum visit (no later than 6 wk after delivery) by medical doctors providing routine care. When the two LMP records differed, the doctor made the final decision on the LMP at the postpartum visit based on other prenatal medical records. PTD was defined as a live birth with <37 completed gestational weeks (WHO 1977).

Definition of PM Exposure

Daily PM$_1$, PM$_2.5$, and PM$_{10}$ concentrations across mainland China during the study period were predicted at a spatial resolution of 0.1° × 0.1° using a machine learning method (Chen et al. 2018a, 2018b, 2018c). Briefly, a random forest model with high predictive accuracy was used to predict daily PM$_1$, PM$_2.5$, and PM$_{10}$ concentrations. The predictions were based on ground monitoring data, satellite remote sensing data [Moderate Resolution Imaging Spectroradiometer aerosol optical thickness data (Collection 6)], meteorological data (e.g., weather, wind speed, temperature, and humidity), and land use information data (e.g., urban cover, forest cover). A 10-fold cross-validation indicated $R^2$ values for daily prediction of 64% for PM$_1$, 83% for PM$_2.5$, and 78% for PM$_{10}$. The root mean squared errors for the daily predictions were 17, 18, and 31 $\mu g/m^3$ for PM$_1$, PM$_2.5$, and PM$_{10}$, respectively. Each woman’s home address at the time of preconception, early pregnancy, and post-delivery was geocoded into latitude and longitude. The three addresses were compared, and 22,956 (1.5%) pregnant women who moved during pregnancy were excluded from the analysis (Figure S1). We linked each address with the predicted daily PM$_1$, PM$_2.5$, and PM$_{10}$ concentrations (Wang et al. 2018) and then estimated gestational age–specific exposures to PM$_1$, PM$_2.5$, and PM$_{10}$ for each woman.

Definition of FA Supplementation

FA supplementation was investigated by questionnaire interview at the early pregnancy visit. In the questionnaire, FA supplementation was categorized as initiated ≥3 months prior to pregnancy, initiated 1–2 months prior to pregnancy, initiated after conception, or never used. According to the recommendation for FA supplementation by the Nationwide Folic Acid Supplementation Program of China (Li et al. 2014; Liu et al. 2015), which also supplies free daily FA pills (400 $\mu g$) to rural woman from 3 months prior to pregnancy to the end of first trimester, we defined the FA supplement status of each woman as a) initiated FA ≥3 months prior to pregnancy; b) initiated FA 1–2 months prior to pregnancy; or c) never used preconception FA.

Statistical Analyses

Cox proportional hazard regression models were used for the analyses, with weeks of gestation as the time scale and spontaneous PTD as the outcome. Observations were censored in the event of induced PTD or fetal death (Slama et al. 2014). Given that preterm births had shorter exposure durations than term births, we fitted time-varying gestational age–specific exposures (Hao et al. 2016). We adjusted for variables that might be associated with PM exposures and PTD (Klepac et al. 2018), including maternal age at delivery (continuous); body mass index (BMI) before conception (continuous); self-reported occupational or nonoccupational exposure to organic solvents, heavy metals, or pesticides (yes or no; queried at the early pregnancy visit); active smoking during pregnancy (classified as none if no active smoking was reported at the preconception visit, quit if smoking was reported at the preconception visit but not at the early pregnancy visit, and current if smoking was reported at the early pregnancy visit); passive smoking during pregnancy (none, quit, or current, defined as for active smoking); and alcohol consumption during pregnancy (none, quit, or current, defined as for active smoking) as covariables in the models. We also adjusted for registered residence (urban or rural), educational level (primary school or below, high school, and college or higher), and occupation [farmer, nonfarm payroll employment, or others (e.g., unemployed, individual business, and other unmentioned occupations)] at the early pregnancy visit because these characteristics were assumed to be associated with both nutritional supplementation (Tang et al. 2017) and pollutant exposure. However, given that they could be correlated, we also conducted sensitivity analyses using separate models to adjust for registered residence, education, and occupation individually. To control for the potential nonlinear effect of ambient temperature during pregnancy, a natural cubic spline of average mean daily temperature during each gestational week of pregnancy at the same spatial resolution of PM was included in the models. We also included a random intercept for each province in the models to control for a potential cluster effect (Wang et al. 2018). Observations with missing covariate data were excluded from the adjusted models. To examine the proportional hazard assumption, we also rebuilt the Cox models by
modeling interactions between gestational week and PM$_1$, PM$_{2.5}$, PM$_{10}$, and FA supplementation, respectively.

To estimate whether FA supplementation modifies the association between PTD and maternal exposure to PM$_1$, PM$_{2.5}$, and PM$_{10}$ during pregnancy, we first estimated the separate effects of FA supplementation and each of the PM exposures after adjusting for the covariates listed above. We then modeled a multiplicative interaction term between FA supplementation (three categories) and gestational week–specific PM exposures (continuous) (Knol and VanderWeele 2012). Next, we estimated the joint effects of FA supplementation (three categories) and gestational week–specific quartiles of PM exposures and used the relative excess risk due to interaction (RERI) to formally evaluate departures from additive interaction models for 10 coastal provinces (considered as developmental areas) and 20 inland provinces (considered as developing areas), respectively. Using a 37-wk cutoff is expected to be sensitive to misclassification of the LMP; therefore, we also estimated multiplicative interactions between FA supplementation and PM on the risk of very PTD, which was defined as a live birth with <32 completed gestational weeks.

Because of potential regional disparities in participant characteristics and PM composition, we fitted separate multiplicative interaction models for 10 coastal provinces (considered as developed areas) and 20 inland provinces (considered as developing areas), respectively. Using a 37-wk cutoff is expected to be sensitive to misclassification of the LMP; therefore, we also estimated multiplicative interactions between FA supplementation and PM on the risk of very PTD, which was defined as a live birth with <32 completed gestational weeks.

All analyses were performed using R (version 3.4.4; R Development Core Team). p-Values of <0.05 were considered statistically significant.

Results

In total, 1,229,556 singleton live births were included in the present study of primiparous Han women from 30 of China’s 31 mainland provinces (Figure 1). Overall, 8.1% of births (98,998) were preterm (Table 1). Compared with women who did not use preconception FA, women who initiated FA ≥3 months prior to pregnancy were slightly older and had a higher BMI on average, were more likely to live in coastal provinces and work as farmers, and were less likely to report passive smoking exposure (Table 2). The incidence of PTD among women who initiated FA ≥3 months prior to pregnancy was 7.3%, compared with 7.6% for women who initiated FA ≥3 months prior to pregnancy and 8.8% for women who did not use preconception FA. Median PM$_1$, PM$_{2.5}$, and PM$_{10}$ exposures during pregnancy were 46.9, 66.9, and 116.9 µg/m$^3$, respectively, among women who initiated FA ≥3 months prior to pregnancy, compared with 45.2, 61.2, and 100.2 µg/m$^3$, respectively, among women who did not use preconception FA. Demographic characteristics of participants who were excluded from the present analysis were comparable with those of the analytic population (Tables S2 and S3).

Compared with women who did not take supplementary FA during preconception, PTD was less likely among women who initiated FA ≥3 months prior to pregnancy (hazard ratio [HR] = 0.77 [95% confidence interval [CI]: 0.76, 0.78]) and women who initiated FA ≥3 months prior to pregnancy (HR = 0.82 [95% CI: 0.81, 0.84]) (Table 3). In addition, pregnant women who had higher PM exposures had a higher risk of PTD than women in the lowest exposure group (below the first quartile), with HRs for women in the highest exposure group (above the third quartile) of 1.29 (95% CI: 1.26, 1.32) for PM$_1$, 1.52 (95% CI: 1.46, 1.58) for PM$_{2.5}$, and 1.22 (95% CI: 1.17, 1.27) for PM$_{10}$. In general, crude HRs for associations with FA and PM exposures were similar to adjusted values (Table S4).

HRs for PTD in association with a 10-µg/m$^3$ increase in PM$_1$ over the entire pregnancy were significantly higher among women who did not use preconception FA [HR = 1.12 (95% CI: 1.11, 1.13)] compared with women who started FA ≥3 months before pregnancy [HR = 1.09 (95% CI: 1.08, 1.10); pinteraction <0.001] (Table 4). Corresponding HRs and 95% CIs were almost identical for a 10-µg/m$^3$ increase in PM$_{2.5}$ according to FA supplementation, indicating a significantly lower risk in women with early preconception FA. HRs for PTD with a 10-µg/m$^3$ increase in PM$_{10}$ were weaker but still indicated a significantly lower risk among

Figure 1. Map of the 30-province study area of mainland China. Tibet was not included in the study because the Han ethnicity there is in the minority.
women with early preconception FA supplementation [HR = 1.03 (95% CI: 1.02, 1.03)] than among women who did not use preconception FA [HR = 1.04 (95% CI: 1.03, 1.04); \( p \text{interaction} < 0.001 \)]. In contrast, associations between PTD and PM were similar between women who did not use preconception FA and women who initiated FA supplementation 1–2 months before pregnancy (\( p \text{interaction} = 0.3–0.8 \)). Crude HRs for multiplicative interactions between FA and PM exposures were consistent to adjusted values (Table S5).

We further estimated additive scale interactions using women in the lowest quartile of PM who initiated FA \( \geq 3 \) months before pregnancy as a common referent group (Table 5). Compared with this group, HRs for PTD among pregnant women with PM2.5 exposures in the highest quartile were 1.61 (95% CI: 1.56, 1.67) for women who did not use preconception FA, compared with 1.21 (95% CI: 1.17, 1.26) for women who started FA \( \geq 3 \) months prior to pregnancy [RERI = 0.18 (95% CI: 0.13, 0.23)]. HRs for PTD in women with combined exposure to no FA and high PM2.5 or high PM10 also suggested synergistic effects, with corresponding RERIs of 0.27 (95% CI: 0.21, 0.30) and 0.15 (95% CI: 0.10, 0.20), respectively. In general, HRs for PM-related PTD among women who started FA 1–2 months before pregnancy were higher than corresponding HRs for women who started FA \( \geq 3 \) months before pregnancy.

Associations between very PTD (\( n = 14,345 \)) and 10-\( \mu \)g/m\(^3\) increases in PM exposures according to FA supplementation were less precise but stronger than corresponding HRs for all PTD (Table S6). HRs for very PTD with a 10-\( \mu \)g/m\(^3\) increase in PM2.5 and PM10 were significantly lower among women who started FA \( \geq 3 \) months before pregnancy compared with women who did not use preconception FA. Evidence of modification by FA was weaker for PM2.5.

Associations between PTD and 10-\( \mu \)g/m\(^3\) increases in PM were weaker among women living in inland provinces (total \( n = 776,723; 57,167 \) PTD) who started FA \( \geq 3 \) months before pregnancy compared with women living in inland provinces who

### Table 1. Maternal and fetal characteristics of participants by birth outcome.

| Characteristics | All (\( n = 1,229,566 \)) | Preterm delivery (\( n = 98,998 \)) | Term birth (\( n = 1,130,568 \)) |
|-----------------|--------------------------|---------------------------------|---------------------------------|
| Age (y) [mean (SD)]\(^a\) | 26.3 (3.7) | 26.4 (3.8) | 26.3 (3.7) |
| Registered residence [\( n \% \)] | | | |
| Rural | 1,160,828 (94.4) | 94,027 (95.0) | 1,066,801 (94.4) |
| Urban | 68,732 (5.6) | 4,971 (5.0) | 63,761 (5.6) |
| Missing | 6 (0.0) | 0 (0.0) | 6 (0.0) |
| Geographic location [\( n \% \)] | | | |
| Coastal provinces | 452,843 (36.8) | 41,831 (42.3) | 411,012 (36.4) |
| Inland provinces | 776,723 (63.2) | 57,167 (57.7) | 719,556 (63.6) |
| Educational level [\( n \% \)] | | | |
| Primary school or below | 781,872 (63.6) | 66,572 (67.2) | 715,300 (63.3) |
| High school | 246,721 (20.1) | 12,583 (12.1) | 168,441 (20.2) |
| College or higher | 181,024 (14.7) | 17,892 (12.7) | 228,829 (14.9) |
| Missing | 19,949 (1.6) | 1,951 (2.0) | 17,998 (1.6) |
| Occupation [\( n \% \)] | | | |
| Farmers | 915,262 (74.4) | 76,620 (77.4) | 838,642 (74.2) |
| Nonfarm payroll employment | 208,024 (16.9) | 5,727 (14.6) | 77,203 (17.1) |
| Others | 82,930 (6.7) | 14,468 (5.8) | 193,556 (6.8) |
| BMI (kg/m\(^2\)) [mean (SD)]\(^b\) | 21.2 (2.8) | 21.3 (3.0) | 21.2 (2.8) |
| Chemical exposure [\( n \% \)] | | | |
| No | 1,221,911 (99.4) | 98,392 (99.4) | 1,123,519 (99.4) |
| Yes | 7,655 (0.6) | 606 (0.6) | 7,049 (0.6) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Active smoking [\( n \% \)]\(^c\) | | | |
| No | 1,214,541 (98.8) | 97,493 (98.5) | 1,117,048 (98.8) |
| Quit | 8,971 (0.7) | 827 (0.8) | 8,144 (0.7) |
| Current | 3,833 (0.3) | 357 (0.4) | 3,476 (0.3) |
| Missing | 2,221 (0.2) | 321 (0.3) | 1,900 (0.2) |
| Drinking [\( n \% \)]\(^d\) | | | |
| No | 1,212,596 (98.6) | 97,390 (98.4) | 1,115,206 (98.6) |
| Quit | 10,453 (0.9) | 895 (0.9) | 9,558 (0.8) |
| Current | 3,551 (0.3) | 314 (0.3) | 3,237 (0.3) |
| Missing | 2,966 (0.2) | 399 (0.4) | 2,567 (0.2) |
| Passive smoking [\( n \% \)]\(^e\) | | | |
| No | 935,448 (76.1) | 75,135 (75.9) | 860,313 (76.1) |
| Quit | 100,811 (8.2) | 8,527 (8.6) | 92,284 (8.2) |
| Current | 191,123 (15.5) | 15,017 (15.2) | 176,106 (15.6) |
| Missing | 2,184 (0.2) | 319 (0.3) | 1,865 (0.2) |
| PM concentrations (\( \mu \)g/m\(^3\)) [median (IQR)]\(^f\) | | | |
| PM2.5 | 46.1 (38.6–52.8) | 45.7 (37.9–53.3) | 46.1 (38.6–52.7) |
| PM10 | 63.4 (50.4–77.2) | 62.3 (49.8–76.3) | 63.5 (50.5–77.3) |

Note: BMI, body mass index; IQR, interquartile range; PM, particulate matter; PM2.5, PM with diameters of \( \leq 1 \) mm; PM10, PM with diameters of \( \leq 2.5 \) mm; PM10, PM with diameters of \( \leq 10 \) mm; SD, standard deviation.  
\(^{a}\)Maternal age at the time of delivery.  
\(^{b}\)BMI measured during preconception health checkup.  
\(^{c}\)Self-report of any occupational or nonoccupational exposure to organic solvents, heavy metals, or pesticides during pregnancy.  
\(^{d}\)No: behavior not reported at the preconception visit; Quit: behavior reported at the preconception visit but not the early pregnancy visit; Current: behavior reported at the early pregnancy visit.  
\(^{e}\)Values based on the overall distribution of gestational week–specific PM concentrations throughout pregnancy.
Table 2. Maternal and fetal characteristics of participants by folic acid (FA) supplementation.

| Characteristics                  | Never used FA during preconception (n = 565,364) | Initiated FA 1–2 months prior to pregnancy (n = 191,187) | Initiated FA ≥3 months prior to pregnancy (n = 473,015) |
|----------------------------------|-----------------------------------------------|---------------------------------------------------|-----------------------------------------------------|
| Age (y) [mean (SD)]a             | 26.1 (3.6)                                    | 26.4 (3.6)                                        | 26.5 (3.7)                                          |
| Registered residence [n (%)]      |                                               |                                                   |                                                     |
| Rural                            | 535,486 (94.7)                                | 178,039 (93.1)                                   | 447,303 (94.6)                                     |
| Urban                            | 29,873 (5.3)                                  | 13,148 (6.9)                                     | 25,711 (5.4)                                       |
| Missing                          | 5 (0.0)                                       | 0 (0.0)                                          | 1 (0.0)                                             |
| Geographic location [n (%)]       |                                               |                                                   |                                                     |
| Coastal provinces                | 193,992 (34.3)                                | 72,618 (38.0)                                    | 186,233 (39.4)                                     |
| Inland provinces                 | 371,372 (65.7)                                | 118,569 (62.0)                                   | 286,782 (60.6)                                     |
| Educational level [n (%)]        |                                               |                                                   |                                                     |
| Primary school or below          | 364,045 (64.4)                                | 114,832 (60.1)                                   | 302,995 (64.1)                                     |
| High school                      | 115,964 (20.5)                                | 39,248 (20.5)                                    | 91,509 (19.3)                                      |
| College or higher                | 76,564 (13.5)                                 | 33,743 (17.6)                                    | 70,717 (15.0)                                      |
| Missing                          | 8,791 (1.6)                                   | 3,364 (1.8)                                      | 7,794 (1.6)                                        |
| Occupation [n (%)]                |                                               |                                                   |                                                     |
| Farmers                          | 415,079 (73.4)                                | 135,883 (71.1)                                   | 364,300 (77.0)                                     |
| Nonfarm payroll employment       | 42,525 (7.5)                                  | 15,015 (7.9)                                     | 25,390 (5.4)                                       |
| Others                           | 96,702 (17.1)                                 | 36,567 (19.1)                                    | 74,755 (15.8)                                      |
| Missing                          | 11,058 (2.0)                                  | 3,722 (1.9)                                      | 8,570 (1.8)                                        |
| BMI (kg/m²) [mean (SD)]b         | 21.1 (2.8)                                    | 21.1 (2.8)                                       | 21.3 (2.8)                                         |
| Chemical exposure [n (%)]c        |                                               |                                                   |                                                     |
| No                               | 562,489 (99.5)                                | 189,546 (99.1)                                   | 469,876 (99.3)                                     |
| Yes                              | 2,875 (0.5)                                   | 1,636 (0.9)                                      | 3,135 (0.7)                                        |
| Missing                          | 0 (0.0)                                       | 0 (0.0)                                          | 0 (0.0)                                             |
| Active smoking [n (%)]d           |                                               |                                                   |                                                     |
| No                               | 559,516 (99.0)                                | 189,187 (99.0)                                   | 465,388 (98.5)                                     |
| Quit                             | 2,929 (0.5)                                   | 1,149 (0.6)                                      | 4,893 (1.0)                                        |
| Current                          | 1,808 (0.3)                                   | 462 (0.2)                                        | 1,563 (0.3)                                        |
| Missing                          | 1,111 (0.2)                                   | 389 (0.2)                                        | 721 (0.2)                                          |
| Drinking [n (%)]d                 |                                               |                                                   |                                                     |
| No                               | 558,305 (98.8)                                | 188,806 (98.8)                                   | 465,485 (98.4)                                     |
| Quit                             | 3,828 (0.7)                                   | 1,473 (0.8)                                      | 5,152 (1.1)                                        |
| Current                          | 1,709 (0.3)                                   | 415 (0.2)                                        | 1,427 (0.3)                                        |
| Missing                          | 1,522 (0.3)                                   | 493 (0.3)                                        | 951 (0.2)                                          |
| Passive smoking [n (%)]d          |                                               |                                                   |                                                     |
| No                               | 421,695 (74.6)                                | 133,280 (69.7)                                   | 380,476 (80.4)                                     |
| Quit                             | 44,804 (7.9)                                  | 16,942 (8.9)                                     | 39,065 (8.3)                                       |
| Current                          | 97,785 (17.3)                                 | 40,579 (21.2)                                    | 52,759 (11.2)                                      |
| Missing                          | 1,080 (0.2)                                   | 386 (0.2)                                        | 718 (0.2)                                          |
| PM concentrations (µg/m³) [median (IQR)]e |                                         |                                                   |                                                     |
| PM₁                              | 45.2 (38.1–51.9)                              | 46.6 (38.1–53.8)                                 | 46.9 (39.5–53.4)                                   |
| PM₂₅                             | 61.2 (50.2–73.6)                              | 63.0 (49.6–76.6)                                 | 66.9 (51.3–80.7)                                   |
| PM₁₀                             | 100.2 (81.4–126.9)                            | 105.2 (83.6–134.1)                               | 116.9 (86.8–141.6)                                 |
| Preterm delivery [n (%)]         |                                               |                                                   |                                                     |
| No                               | 515,507 (91.2)                                | 176,578 (92.4)                                   | 438,483 (92.7)                                     |
| Yes                              | 49,857 (8.8)                                  | 14,609 (7.6)                                     | 34,532 (7.3)                                       |

Note: BMI, body mass index; IQR, interquartile range; PM, particulate matter; PM₁, PM with diameters of ≤1 µm; PM₂₅, PM with diameters of ≤2.5 µm; PM₁₀, PM with diameters of ≤10 µm; SD, standard deviation.

*aMale age at the time of delivery.

*bBMI measured during preconception health checkup.

cSelf-report of any occupational or nonoccupational exposure to organic solvents, heavy metals, or pesticides during pregnancy.

*dNo: behavior not reported at the preconception visit; Quit: behavior reported at the preconception visit but not the early pregnancy visit or quit active smoking, passive smoking, or drinking after conception; Current: behavior reported at the early pregnancy visit.

*eValues based on the overall distribution of gestational week-specific PM concentrations throughout pregnancy.

Discussion

To the best of our knowledge, this is the first study to examine the modification of the association between maternal exposure to PM and PTD by FA supplementation. We analyzed a national cohort of more than 1.2 million primiparas of Han ethnicity in mainland China and observed significant interactions between FA supplementation and PM exposure on the risk of PTD at both multiplicative and additive scales. More specifically, we found that the increased risk of PTD associated with PM₁, PM₂₅, and PM₁₀ exposure during pregnancy was significantly lower among participants who had used FA before conception compared to those who did not use FA before conception. Our findings highlight the importance of FA supplementation in reducing the risk of PTD, especially in areas with high PM exposure. Further studies are needed to investigate the mechanisms underlying these interactions and to explore strategies for optimizing FA supplementation in high-exposure settings.
Table 3. Separate effect estimates for maternal folic acid (FA) supplementation and time-varying particulate matter concentrations on the risk of preterm delivery among 1,190,455 singleton pregnancies (93,657 preterm deliveries) with complete covariate data.

| Categories | Hazard ratio | 95% CI |
|------------|--------------|--------|
| FA supplementation status | | |
| Never used FA during preconception | Ref | — |
| Initiated FA 1–2 months prior to pregnancy | 1.09 (1.08, 1.10) | <0.001 |
| Initiated FA ≥3 months prior to pregnancy | 1.06 (1.05, 1.07) | <0.001 |
| PM1 percentile | | |
| <25th | Ref | — |
| 25th–50th | 1.12 (1.11, 1.14) | 0.001 |
| >50th–75th | 1.13 (1.11, 1.14) | 0.273 |
| >75th | 1.09 (1.08, 1.10) | <0.001 |
| PM10 percentile | | |
| <25th | Ref | — |
| 25th–50th | 1.12 (1.11, 1.14) | 0.001 |
| >50th–75th | 1.13 (1.11, 1.14) | 0.273 |
| >75th | 1.09 (1.08, 1.10) | <0.001 |

Note: Cox proportional hazard regression with gestational weeks as the time scale and a random intercept for province, adjusted for maternal age at delivery, registered residence, educational level, occupation, preconception BMI, chemical exposure, active and passive cigarette smoking, alcohol consumption, and average daily mean temperature (time-varying by gestational week, natural cubic spline). PM concentrations were modeled as time-varying average values for each gestational week, with percentiles based on the distribution of average exposures over all gestational weeks. BMI, body mass index; CI, confidence interval; PM, particulate matter; PM1, PM with diameters of ≤1 μm; PM10, PM with diameters of ≤10 μm; Ref, reference.

Table 4. Adjusted hazard ratios for preterm delivery in association with a 10-mg/m³ increase in time-varying PM concentrations according to maternal folic acid (FA) supplementation (1,190,455 singleton pregnancies, 93,657 preterm deliveries).

| Categories | HR (95% CI) | Pinteraction |
|------------|-------------|--------------|
| PM1 | | |
| Never used FA during preconception | 1.12 (1.11, 1.13) | — |
| Initiated FA 1–2 months prior to pregnancy | 1.12 (1.11, 1.13) | 0.001 |
| Initiated FA ≥3 months prior to pregnancy | 1.09 (1.08, 1.10) | <0.001 |
| PM10 | | |
| Never used FA during preconception | 1.12 (1.11, 1.13) | — |
| Initiated FA 1–2 months prior to pregnancy | 1.13 (1.11, 1.14) | 0.273 |
| Initiated FA ≥3 months prior to pregnancy | 1.09 (1.08, 1.10) | <0.001 |

Note: Cox proportional hazard regression with gestational weeks as the time scale, a random intercept for province, and multiplicative interaction terms between PM concentrations (continuous) and FA supplementation, adjusted for maternal age at delivery, registered residence, educational level, occupation, preconception BMI, chemical exposure, active and passive cigarette smoking, alcohol consumption, and average daily mean temperature (time-varying by gestational week, natural cubic spline). PM concentrations were modeled as time-varying average values for each gestational week. —, not applicable; BMI, body mass index; CI, confidence interval; HR, hazard ratio; PM, particulate matter; PM1, PM with diameters of ≤1 μm; PM10, PM with diameters of ≤10 μm; Ref, reference.

Pregnant women who initiated FA ≥3 months prior to pregnancy in comparison with women who did not use preconception FA. These findings provide supportive evidence for policy makers to improve guidelines regarding FA supplementation for pregnancy, especially among women exposed to high levels of air pollution.

It is difficult to compare our findings with those of previous studies because, to our knowledge, this is the first study to suggest that FA supplementation may help reduce the risk of PTB in association with PM exposure during pregnancy. However, a case–control study with more than 6,000 pregnancies conducted in the United States reported that pregnant women with higher traffic-related air pollution exposure levels and lower intakes of methyl nutrients (e.g., FA) before conception had a higher risk of congenital heart defects than those with lower exposure levels and higher methyl nutrient intakes, with an odds ratio of 3.32 (95% CI: 1.74, 6.01) and an RERI of 2.15 (95% CI: 0.39, 3.92) (Stingone et al. 2017). A longitudinal study of 549 participants reported that associations between PM2.5 and cardiac autonomic dysfunction were weaker in participants with higher intakes (above median levels) of methyl nutrients, compared with those who had lower methyl nutrient intakes (Baccarelli et al. 2008).

We are not aware of direct evidence regarding biological mechanisms for a protective effect of FA supplementation on the association between PM exposure and PTB. However, a longitudinal study of 240 newborns reported that PM2.5 exposure in early pregnancy was associated with lower total DNA methylation levels in placental tissues (Janssen et al. 2013). Another case–control study of 187 mother–newborn pairs reported associations between methylation in peripheral blood samples collected after pregnancy and the odds of previously having given birth to a child with congenital heart disease (Chowdhury et al. 2011). A previous study also reported evidence suggesting that epigenetic reprogramming of placental-specific genes may be important for the regulation of placental and fetal growth (Constância et al. 2002). Thus, it is plausible that pathways related to DNA methylation levels may underlie associations between PM exposure and PTB.

It is well known that FA acts as an essential coenzyme and methyl donor that can regulate the process of DNA methylation (Zeisel 2009). An experimental study indicated that FA supplementation can mitigate PM2.5 toxicity in zebrafish embryos by targeting aryl hydrocarbon receptor and Wnt/β-catemin signal pathways, which are related to DNA methylation modulation (Yue et al. 2017). A crossover trial of 10 healthy adults that compared genome-wide methylation in peripheral CD4+ Th cells following a 2-h exposure to PM2.5 at 250 μg/m³ before and after 4 wk of B vitamin supplementation reported that PM2.5 exposure modified DNA methylation in the top 10 individual CpG sites, whereas B vitamin (e.g., FA) supplementation seemed to inhibit these changes (Pinteraction = 0.001) (Zhong et al. 2017). A case–control study reported evidence suggesting that maternal intake of methyl nutrients may modify associations between traffic-related air pollution and congenital perimembranous ventricular septal defects (Stingone et al. 2017). These findings suggest that FA might have a protective effect on PM-related PTB by regulating DNA methylation levels as an essential coenzyme and methyl donor.

Beyond epigenetics, reactive oxygen species production and oxidative stress is a well-documented mechanism for the adverse health effects of inhaled PMs (Mazzoli-Rocha et al. 2010). Studies of maternal PM exposure and PTB have suggested that oxidative stress could be a potential biological pathway (Moore et al. 2018; Li et al. 2017; Pereira et al. 2014). A randomized clinical trial of 438 healthy adults compared urine 8-hydroxy-2′-deoxyguanosine (8-OHdG/Cr), a marker of oxidative damage to DNA, before and after intervention among three groups—a) FA at 0.4 mg/d for 8 wk; b) FA at 0.8 mg/d for 8 wk; and c) placebo for 8 wk—and found that urinary 8-OHdG/Cr levels were decreased in a dose-related pattern for participants who had FA supplementation (Guo et al. 2015). These findings suggest that FA might have a protective effect on PM-related PTB by regulating the imbalance of oxidants and antioxidants as an antioxidant.

FA concentrations in the circulation are important in regulating DNA methylation and maintaining the balance of oxidants and antioxidants. A previous study reported that blood FA concentrations declined as pregnancy advanced (Pickell et al. 2011).
However, preconception FA supplementation can prevent the natural decline (Bailey 2009) because FA has a half-life of 100 d (Tamura and Picciano 2006). As a whole, evidence from experimental and observational studies suggests that preconception FA supplementation may protect against PM-related PTD. However, further studies are needed to confirm and clarify the mechanisms underlying the interaction between FA and PM exposure on PTD.

In 2009, the Chinese government launched a nationwide program, supplying free daily FA pills to pregnant women in rural areas beginning 3 months prior to pregnancy through the first trimester. This may explain why women who worked as farmers were more likely than other women to have initiated FA supplementation ≥3 months prior to pregnancy. However, only 38.1% of women in our overall study sample had initiated FA ≥3 months prior to pregnancy. An epidemiological survey conducted in China during 2011–2012 reported that only one-fifth to two-fifths of the women started taking FA supplements before their LMP (Liu et al. 2015). The authors suggested that many women may not be aware that they are pregnant before the end of the first trimester, which may explain why preconception and first trimester FA supplementation is uncommon (Liu et al. 2015). Thus, we recommend that local governments take additional measures to publicize the importance of preconception planning, including initiating FA supplementation before 3 months prior to pregnancy.

Several limitations of our study should be acknowledged. First of all, even though we used daily PM1, PM2.5, and PM10 concentrations predicted by satellite remote sensing information to evaluate each pregnant woman’s PM exposure, there may have been misclassification of exposures owing to variabilities at the microenvironmental level (e.g., within community or indoor pollution, household cooking fuel, neighboring traffic density), which cannot be captured by this method (Padula et al. 2014). Although we adjusted for occupation (farmer, nonfarm payroll employment, or others) and registered residence (urban or rural), which may partly offset differences in time–activity patterns and traffic exposures, there may still be bias due to exposure misclassification.

Second, the use of self-reported LMPs to estimate gestational age may result in some outcome misclassification. Although we censored observations for preterm deliveries that were known to be induced due to medical complications, we cannot be certain that all preterm births included in the analysis were spontaneous.

Third, our study population was limited to women of Han ethnicity, which accounts for only 1 of 56 ethnic groups in China but 92% of the mainland Chinese population. Differences in diets, customs, and activities among women in minority ethnic groups may affect potential modification of associations between PM and PTD by FA supplementation; thus, additional studies are needed to determine if our findings are generalizable to non-Han women. In addition, although we included a random intercept for province and compared estimates between women in coastal and inland provinces, we cannot rule out residual confounding by region.

Last, we did not have information on specific FA doses or the exact dates when supplements were initiated and discontinued, and thus we could not estimate the modification of associations between PM and PTD according to doses or duration of use. However, it is likely that most of the women who used FA supplements took 400 μg of FA daily and stopped at the end of first trimester, in accordance with the Nationwide Folic Acid Supplementation Program of China (Liu et al. 2015). Owing to the observational design, we cannot entirely exclude the possibility that FA supplementation could be a marker of unmeasured factors that may confound the observed protective effect. The differences in apparent modification of PM–PTD associations according to the timing of preconception FA initiation do not necessarily indicate a causal effect of earlier vs. later initiation only. Future clinical trials are warranted to confirm our findings.

**Conclusion**

Exposure to PM1, PM2.5, and PM10 during pregnancy was associated with an increased risk of PTD. However, the associations were significantly weaker among women who initiated FA supplementation ≥3 months prior to pregnancy than among women who did not use FA supplements before pregnancy. Given the high PM exposure levels and the heavy burden of PTD in China, our findings suggest that encouraging FA supplementation among women planning for pregnancy may have substantial benefits, especially for women residing in areas with high levels of air pollution.

**Acknowledgments**

Q.L., Y.-Y.W., and Y.G. designed the study, interpreted the results, and drafted the manuscript. H.Z. and X.W. drafted and

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**Table 5.** Additive scale interactions between maternal folic acid (FA) supplementation and time-varying particulate matter concentrations on the risk of preterm delivery (1,190,455 singleton pregnancies, 93,657 preterm deliveries).

| Exposure level | Initiated FA >3 months prior to pregnancy (G0) [HR (95% CI)] | Initiated FA 1–2 months prior to pregnancy (G1) [HR (95% CI)] | Never used FA during preconception (G2) [HR (95% CI)] | RERI (G1 vs. G0) (95% CI) |
|---------------|-------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------|--------------------------|
| **PM1 percentile** | | | | |
| <25th | Ref | 0.98 (0.94, 1.02) | 1.22 (1.19, 1.25) | — | — |
| 25th–50th | 1.10 (1.06, 1.13) | 1.17 (1.12, 1.22) | 1.47 (1.42, 1.51) | 0.10 (0.04, 0.16) | 0.15 (0.11, 0.20) |
| >75th | 1.21 (1.17, 1.26) | 1.32 (1.26, 1.38) | 1.51 (1.47, 1.56) | 0.18 (0.12, 0.25) | 0.14 (0.09, 0.18) |
| **PM2.5 percentile** | | | | |
| <25th | Ref | 0.99 (0.96, 1.03) | 1.20 (1.16, 1.23) | — | — |
| 25th–50th | 1.23 (1.19, 1.28) | 1.27 (1.22, 1.33) | 1.64 (1.58, 1.69) | 0.05 (−0.01, 0.11) | 0.21 (0.16, 0.26) |
| >75th–50th | 1.32 (1.27, 1.38) | 1.41 (1.35, 1.48) | 1.75 (1.68, 1.82) | 0.10 (0.03, 0.16) | 0.23 (0.17, 0.28) |
| >75th | 1.40 (1.34, 1.46) | 1.66 (1.57, 1.75) | 1.87 (1.78, 1.95) | 0.27 (0.20, 0.34) | 0.27 (0.21, 0.30) |
| **PM10 percentile** | | | | |
| <25th | Ref | 1.01 (0.97, 1.05) | 1.21 (1.17, 1.24) | — | — |
| 25th–50th | 1.06 (1.04, 1.12) | 1.07 (1.02, 1.12) | 1.40 (1.35, 1.44) | −0.02 (−0.08, 0.04) | 0.11 (0.07, 0.16) |
| >50th–75th | 1.05 (1.01, 1.10) | 1.15 (1.09, 1.20) | 1.45 (1.40, 1.51) | 0.08 (0.02, 0.14) | 0.19 (0.15, 0.24) |
| >75th | 1.15 (1.09, 1.20) | 1.34 (1.27, 1.41) | 1.50 (1.43, 1.57) | 0.18 (0.12, 0.24) | 0.15 (0.10, 0.20) |

Note: Cox proportional hazard regression with gestational weeks as the time scale and a random intercept for province, adjusted for maternal age at delivery, registered residence, educational level, occupation, preconception BMI, chemical exposure, active and passive cigarette smoking, alcohol consumption, and average daily mean temperature (time-varying by gestational week, natural cubic spline). PM concentrations were modeled as time-varying average values for each gestational week, with percentiles based on the distribution of average exposures over all gestational weeks. —, not applicable; BMI, body mass index; CI, confidence interval; G0, initiated FA >3 months prior to pregnancy (group); G1, initiated FA 1–2 months prior to pregnancy (group); G2, never used FA during preconception (group); HR, hazard ratio; PM, particulate matter; PM1, PM with diameters of ≤2.5 μm; PM2.5, PM with diameters of 2.5–10 μm; Ref, reference; RERI, relative excess risk due to interaction on an additive scale.
revised the manuscript. S.L. and G.C. contributed to the exposure assessment. Q.-M.W., H.-P.S., Y.-P.Z., D.-H.Y., Y.-H.Y., and Z.-Q.P. collected the data and revised the manuscript. H.-J.W. and X.M. conceived of the study, supervised the study, interpreted the results, and approved the final manuscript. All authors contributed to the critical reading of, and commented on, the manuscript; helped interpret the data; and approved the final manuscript.

The manuscript’s guarantors (H.-J.W. and X.M.) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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