Particulate matter may have a limited influence on maternal vitamin D levels

Chong Li1, Ya-qin Gong2, Yun-yu Xia3, Xiao-chun Wang3, Lin Chen4, Shan-jun Yan4, Rong-zhu Lu5 & Ke Lu1*

Evidence for an association between the amount of particulate matter (PM) in the atmosphere and vitamin D status of pregnant women is limited. We aimed to examine the independent association between PM and maternal levels of serum 25-hydroxyvitamin D (25OHD) during the second trimester and to explore possible modifications to the association by meteorological factors. 27,768 pregnant women presenting for prenatal examination who were tested for serum 25OHD concentration during the second trimester between January 1, 2016, and December 31, 2020, were included in this retrospective analysis. Exposure to PM was evaluated based on daily average PM with an aerodynamic diameter of ≤ 2.5 μm (PM2.5) and PM with an aerodynamic diameter of ≤ 10 μm (PM10). Corresponding meteorological data for daily average atmospheric temperature, atmospheric pressure, relative humidity, sunshine duration, and wind speed were collected. The maximum cumulative effects of PM2.5 occurred at lag 45 days, and the maximum cumulative effects of PM10 occurred at lag 60 days. In crude models, 45-day moving daily average PM2.5 concentrations were negatively associated with 25OHD levels (β, −0.20; 95% CI −0.21 to −0.19), as were 60-day moving daily average PM10 concentrations (β, −0.14; 95% CI −0.15 to −0.14). After adjusting for temporal and meteorological factors, the effect values were drastically reduced (adjusted β of PM2.5, −0.032; 95% CI −0.046 to −0.018; adjusted β of PM10, −0.039; 95% CI −0.049 to −0.028). Our study showed there was a small, independent, negative association between PM in the atmosphere and maternal serum 25OHD levels during the second trimester of pregnancy after adjusting for temporal and/or meteorological factors, which indicates that PM may have a limited influence on maternal serum 25OHD levels. Besides taking vitamin D supplements, pregnant women should keep participating in outdoor activities while taking PM protection measures to improve their vitamin D levels when PM levels are high in winter and spring.

The key fat-soluble nutrient vitamin D has multiple functions, and its deficiency is thought to be a risk factor in skeletal health and various non-skeletal conditions, such as schizophrenia, skin disorders, certain types of cancer, type 2 diabetes, and infections. For pregnant women, sufficient vitamin D stores need to be maintained to provide for both themselves and their fetus. Research continues to provide evidence of an association between maternal vitamin D deficiency (VDD) and a higher risk of numerous undesirable pregnancy outcomes, such as a low body weight, respiratory tract infections, and neurocognitive developmental problems in newborns and preeclampsia and high blood pressure in mothers. Therefore, VDD is a key clinical issue for pregnant women and deserves research attention. Throughout the world at present, VDD during pregnancy is still a frequent occurrence. In one study of pregnant women in Finland, 77.4% were found to suffer from VDD (25-hydroxyvitamin D [25OHD] < 50 nmol/L) during their first trimester. While in the USA, Ginde et al. reported 46%, 32%, and 18% of women with VDD (25OHD < 50 nmol/L) in the first, second, and third trimesters, respectively, and there were comparable observations among British, Indian, and Chinese women.

For the most part, factors determining the vitamin D status during pregnancy do not differ from those important for the general population, such as the number of melanocytes in the skin, the amount of exposure of

1Department of Orthopedics, Affiliated Kunshan Hospital of Jiangsu University, No. 91 West of Qianjin Road, Suzhou 215300, Jiangsu, China. 2Information Department, Affiliated Kunshan Hospital of Jiangsu University, Suzhou 215300, Jiangsu, China. 3Meteorological Bureau of Kunshan City, Suzhou 215337, Jiangsu, China. 4Ecology and Environment Bureau of Kunshan City, Suzhou 215300, Jiangsu, China. 5Department of Preventive Medicine and Public Health Laboratory Science, School of Medicine, Jiangsu University, 301 Xuefu Road, Zhenjiang 212013, Jiangsu, China. *email: sgu8434@sina.com
the skin to the sun, the amount of adipose tissue in the body, geographical latitude, dietary factors, and intake of supplementary vitamins\(^\text{14-18}\). An indoor lifestyle can also increase the risk of developing a VDD\(^\text{19}\). Moreover, the amount of PM in the atmosphere has been associated with circulating levels of 25OHD in humans\(^\text{20-23}\), including pregnant women\(^\text{24}\).

It is not yet clear what mechanisms coordinate the links between maternal vitamin D and air pollution levels. Because vitamin D is a relatively scarce resource in food, humans generally rely on the vitamin D produced by cells in the skin on exposure to natural solar ultraviolet (UV) B radiation\(^\text{25,26}\). Some scholars have hypothesized that the reduction in the amount of solar UVB radiation reaching ground level by particulate matter (PM) is the main mechanism linking PM to circulating 25OHD levels in humans\(^\text{23,24}\). In an investigation into the relationship between certain pollutants and ground-level UVB intensity, PM with an aerodynamic diameter of \(\leq 10 \text{ μm} (\text{PM}_{10})\) was shown to be a significant negative predictor of solar UVB radiation, but the impact of \(\text{PM}_{2.5}\) was very small\(^\text{27}\). In addition, vitamin D status correlated with temporal and meteorological factors. During their second trimester, the 25OHD levels of women in eastern China demonstrated variation with season and air temperature\(^\text{28}\). Another study reported 25OHD levels were positively correlated with the prior month's temperature\(^\text{29}\). Thus, when exploring the independent association between PM and vitamin D status, meteorological factors may need to be taken into account.

Thus, our study objective was to examine the independent association between PM and maternal serum 25OHD levels during the second trimester in pregnant women and to explore if meteorological factors have an impact on this association.

**Methods**

**Study population.** We designed a single-hospital-based cross-sectional retrospective observational study to test our hypotheses. All prenatal examination data were collected from the hospital medical database in Affiliated Kunshan Hospital of Jiangsu University located in Kunshan, eastern China, at 31.2° N latitude and approximately 30 km from Shanghai. This is the largest hospital that provides prenatal care in all the districts of Kunshan. Consecutively, 35,476 pregnant women at the 15–20th week gestation (during the second trimester) who visited our institution for prenatal examination and were tested for serum 25OHD concentrations between January 1, 2016, and December 31, 2020, were included in this study. We excluded 7708 women for the following reasons: those (1) with a chronic metabolic disease with consequences for the metabolism of vitamin D (\(n = 5389\)); (2) with a high-risk pregnancy (\(n = 1087\)), or (3) who had lived in Kunshan for less than 1 year (\(n = 1232\)). Finally, 27,768 pregnant women were included in this analysis (Fig. S1).

The study protocol, submitted for review by the ethical committee at the Affiliated Kunshan Hospital of Jiangsu University (approval No. 2020-03-046-K01), was approved, and it complied with the Declaration of Helsinki. Patient information was initially documented for hospital’s quality improvement purposes. The blood samples used for measuring 25OHD were taken as part of prenatal examinations. The requirement for informed consent was waived because of the anonymous and observational design of this investigation. Data analyzers were blinded to the identity of the patients.

**Measurement of vitamin D.** In humans, the most abundant form of vitamin D in the blood is 25OHD, and serum levels are used to reliably estimate a patient's vitamin D status. All pregnant women in this study were in their 15–20th week of gestation (during the second trimester of pregnancy) and were asked to fast before blood samples were taken. Serum 25OHD concentrations were measured immediately using an automated electrochemiluminescence immunoassay on a Roche Cobas 8000/6e602 analyzer (Roche Diagnostics, Mannheim, Germany). There is no medical consensus regarding the status cut-off values of 25OHD concentrations. However, the Institute of Medicine (National Academy of Sciences, Washington, DC, USA) and the National Osteoporosis Society (Bath, England) concur that, for bone health, a serum 25OHD level (2.5 nmol/L 25OHD = 1 ng/mL) of < 30 nmol/L (12 ng/mL) is deficient, 30–50 nmol/L (12–20 ng/mL) is insufficient for certain individuals, while > 50 nmol/L (20 ng/mL) is sufficient for most people\(^\text{30,31}\). The time of blood collection was included in the analysis. Seasons were defined as: Spring, March–May; Summer, June–August; Autumn, September–November; Winter, December–February.

**PM exposure and meteorological data assessment.** We received data for the daily average concentration of PM with an aerodynamic diameter of \(\leq 2.5 \text{ μm} (\text{PM}_{2.5}; \mu \text{g/m}^3)\) and \(\text{PM}_{10} (\mu \text{g/m}^3)\) from the Meteorological Bureau of Kunshan City. Meteorological data (daily average atmospheric temperature [°C], atmospheric pressure [hPa], relative humidity [%], sunshine duration [hour], and wind speed [m/s]) were obtained from the Ecology and Environment Bureau of Kunshan City. The distances between the three environmental (No. 2 Middle School monitoring site, Zhenchuan Middle School monitoring site, and Kunshan Deng-yun College monitoring site) and one meteorological (National Meteorological Observing Station) monitoring site and the hospital are within 11 km. Kunshan City covers an area of 927.7 square kilometers; this distance is shorter than that used for sensitivity analysis in the study by Di et al. in 2017\(^\text{32}\).

Because the serum 25OHD half-life is about 15 days\(^\text{33}\), the cumulative effects of \(\text{PM}_{2.5}\) and \(\text{PM}_{10}\) on maternal serum 25OHD levels during the second trimester of pregnancy were approximated using the moving-average lag structures (blood collection day [day 0] was not included) as follows: 0–3 days (3-day moving daily average PM concentration), 0–7 days (7-day moving daily average PM concentration), 0–15 days (15-day moving daily average PM concentration), 0–30 days (30-day moving daily average PM concentration), 0–45 days (45-day moving daily average PM concentration), 0–60 days (60-day moving daily average PM concentration), 0–75 days (75-day moving daily average PM concentration), and 0–90 days (90-day moving daily average PM concentration).
When adjusting for the influence of meteorological factors, the corresponding moving average lag structures for the meteorological factors were calculated.

**Statistics.** The summary statistics for the characteristics of pregnant women were expressed as frequencies (proportions) for categorical variables and as the means (standard deviation [SD]) or medians (Q1–Q3) for continuous variables. We also conducted univariate logistic regression analysis to evaluate the association between the characteristics of pregnant women and maternal serum 25OHD concentrations during the second trimester. The daily average meteorological variables and daily average PM$_{2.5}$, PM$_{10}$, and 25OHD concentrations were screened for correlations by Pearson’s.

Using generalized estimating equations (GEE), we evaluated the relationships between the cumulative effects of PM on maternal serum 25OHD levels. The cumulative effects of PM were divided into four levels on the basis of quartiles. After adjusting for year and age at blood collection (adjust 1) or year, season, and age at blood collection (adjust 2), β-values (95% confidence interval [CI]) of the maternal serum 25OHD levels were calculated based on group trends. As part of the sensitivity analysis, we also calculated the β-values (95% CI) for the 25OHD levels when using the concentrations of PM$_{2.5}$ and PM$_{10}$ as continuous variables.

Controlling for the influence of meteorological covariates by applying multivariate linear regression analysis allowed us to evaluate independent associations between the maximum cumulative effects of PM and maternal serum 25OHD. We calculated the results of the unadjusted or minimally adjusted analysis and those from fully adjusted analysis. First, collinearity diagnosis of covariates was performed using variance inflation factor (VIF) analysis (the variable average atmospheric temperature was first removed due to VIF > 10). Then, a judgement on whether to adjust covariates was made using the following principles: Criteria 1, the covariate is added to the basic model or removed from the full model and the matched odds ratio (OR) is changed by at least 10%; Criteria 2: Criteria 1 or a covariate P-value of < 0.1 in the univariate model. As part of the sensitivity analysis, we transformed 25OHD quantitative variables into dichotomous qualitative variables (1 = vitamin D deficiency and inadequacy [< 20 ng/mL]; 0 = adequacy [≥ 20 ng/mL]), then the OR and 95% CI for maternal vitamin D deficiency and inadequacy (< 20 ng/mL) associated with a 10 μg/m$^2$ increase in PM$_{2.5}$ or PM$_{10}$ was determined.

Non-linear relationships were additionally identified via a generalized additive model (GAM), and on finding a non-linear correlation, the threshold effect in terms of the smoothing curve was calculated using a two-piecewise linear regression model. When a clear ratio was apparent in the smoothing curve, the recursive method was applied to automatically calculate the turning point at which to use the maximum likelihood model. In addition, to test the robustness and potential variation in the different subgroups, we repeated the subgroup analyses while stratifying by season, age, and meteorological factors. The age threshold was derived from the turning point calculated by the GAM followed by an inspection of the modification and interaction of the subgroups with the likelihood ratio test.

All statistical analyses were performed using the Empower Stats (www.empowerstats.com, X&Y solutions, Inc., Boston, MA, USA) and R software version 3.6.3 (http://www.r-project.org). A P-value < 0.05 was set as the significance threshold.

**Ethics approval.** This study complies with the Declaration of Helsinki and has been approved by the Ethics Committee of the First People’s Hospital of Kunshan (no. 2020-03-046-K01).

**Results** Table 1 displays the data on the pregnant women and their vitamin D statuses. This analysis included 27,768 individuals with a mean age of 28.86 (SD, 4.27) years. The mean (SD) and median (Q1–Q3) values of maternal serum 25OHD concentrations during the second trimester of pregnancy were 17.7 (7.9) ng/mL and 16.0 (12.0–22.0) ng/mL, respectively. Vitamin D deficiency, inadequacy, and adequacy were present in 23.5%, 41.3%, and 35.2% of women, respectively. Univariate logistic regression analysis revealed that maternal 25OHD concentration was positively associated with maternal age and showed seasonal variation, with the peak in September and the nadir in February.

Pearson’s correlation analysis was conducted to compare serum 25OHD concentration, meteorological variables, and air pollutant exposure. Figure S2 presents that, except PM$_{2.5}$ vs. sunshine duration (P-value = 0.82), all correlations among the variables were statistically significant (P-value < 0.001). There was a strong positive correlation between the daily average PM$_{2.5}$ concentration and PM$_{10}$ concentration, and the Pearson coefficient was 0.92. There was also a strong negative correlation between daily average atmospheric temperature and atmospheric pressure, and the Pearson coefficient was −0.89. There was a moderate negative correlation between daily sunshine duration and relative humidity, and the correlation coefficient was −0.68.

Figure 1 shows periodic changes in the above indicators in terms of monthly average values over time. It can be seen that the variation in the average temperature of the last month was most consistent with the periodic variation of monthly average serum 25OHD concentrations. Similar periodic changes were seen for sunshine duration and relative humidity. However, monthly average PM$_{2.5}$ and PM$_{10}$ concentrations and atmospheric pressure showed periodic changes that were diametrically opposite to those of the monthly average serum 25OHD concentration.

Figure 2 and Table S1 show the cumulative effects of PM$_{2.5}$ and PM$_{10}$ on maternal serum 25OHD levels during the second trimester of pregnancy. After we adjusted for year, season, and age at blood collection, the maximum cumulative effects occurred at lag 0–45 days of PM$_{2.5}$ and lag 0–60 days of PM$_{10}$. When PM concentrations were used as continuous variables, similar results were observed, and these are provided in Table S2.

The independent associations between the maximum cumulative effects of PM and serum 25OHD levels were further investigated, and Table 2 shows the results adjusted for different covariances. In the crude models,
the effect sizes of PM$_{2.5}$ ($\beta$, −0.20; 95% CI −0.21 to −0.19; $P$-value < 0.00001) and PM$_{10}$ ($\beta$, −0.14; 95% CI −0.15 to −0.14; $P$-value < 0.00001) were relatively high. After adjustments for year, season, and age at blood collection (Model 1), the effect sizes of PM$_{2.5}$ ($\beta$, −0.11; 95% CI −0.13 to −0.10; $P$-value < 0.00001) and PM$_{10}$ ($\beta$, −0.090; 95% CI −0.099 to −0.081; $P$-value < 0.00001) were reduced. On the basis of the Model 1 adjustment, the effect values of PM$_{2.5}$ ($\beta$, −0.042; 95% CI −0.055 to −0.028; $P$-value < 0.00001) and PM$_{10}$ ($\beta$, −0.039; 95% CI −0.049 to −0.028; $P$-value < 0.00001) were further reduced after adding atmospheric pressure adjustment (Model 2). After further adjustment for sunshine duration, the effect values of Model 3 were similar to those of Model 2. In the fully adjusted Model 4 (adjusted for year, age, season, daily average atmospheric pressure, sunshine duration, relative humidity, and wind speed), there was a negative relationship between the 45-day moving daily average PM$_{2.5}$ concentration and the women’s 25OHD levels ($\beta$, −0.032; 95% CI −0.046 to −0.018; $P$-value < 0.00001), and the 60-day moving daily average PM$_{10}$ concentration was negatively associated with 25OHD levels ($\beta$, −0.039; 95% CI −0.049 to −0.028; $P$-value < 0.00001). As part of the sensitivity analysis, the crude and adjusted OR for PM exposure’s association with maternal vitamin D deficiency and inadequacy (< 20 ng/mL) were determined, which are given in Table S3. We observed greater odds of maternal vitamin D deficiency and inadequacy (< 20 ng/mL) with higher PM levels. In the fully adjusted Model 4, an increase in the PM$_{2.5}$ 45-day moving daily average concentration was associated with a 0.032 ng/mL decrease in 25OHD levels ($P$-value < 0.00001).

Table 1. Characteristics of study participants (N = 27,768). 25OHD 25-hydroxy vitamin D, OR odds ratio, CI confidence interval, SD standard deviation. *Crude associations with maternal serum 25OHD concentrations during pregnancy continuous.

| Characteristics | Statistics | 25OHD, mean (SD), ng/mL | $\beta$ (95% CI)* | $P$-value* |
|-----------------|------------|------------------------|------------------|-----------|
| Maternal serum 25OHD concentrations during pregnancy continuous, mean (SD) | 17.7 (7.9) | 16.0 (12.0–22.0) | |
| Maternal serum 25OHD concentrations during pregnancy categorical, N (%) | |
| Deficiency (< 12 ng/mL) | 6532 (23.5%) | |
| Inadequacy (≥ 12, < 20 ng/mL) | 11,465 (41.3%) | |
| Adequacy (≥ 20 ng/mL) | 9771 (35.2%) | |
| Age tertile, N (%) | |
| Tertile 1 (15–26 years) | 8605 (30.99%) | 17.18 (7.70) | 0.39 (0.15, 0.63) | 0.001 |
| Tertile 2 (27–29 years) | 7948 (28.62%) | 17.57 (7.85) | 0.90 (0.68, 1.12) | < 0.0001 |
| Tertile 3 (30–47 years) | 11,215 (40.39%) | 18.08 (8.03) | |
| $P$ for trend | |
| Year of blood collection, N (%) | |
| 2016 | 5943 (21.40%) | 16.28 (7.45) | |
| 2017 | 7410 (26.69%) | 18.10 (7.65) | 1.82 (1.55, 2.08) | < 0.0001 |
| 2018 | 5616 (20.22%) | 17.68 (8.52) | 1.40 (1.11, 1.68) | < 0.0001 |
| 2019 | 5204 (18.74%) | 18.38 (7.96) | 2.10 (1.81, 2.39) | < 0.0001 |
| 2020 | 3595 (12.95%) | 17.94 (7.65) | 1.65 (1.33, 1.98) | < 0.0001 |
| $P$ for trend | < 0.0001 |
| Month of blood collection, N (%) | |
| January | 2161 (7.78%) | 13.83 (7.02) | |
| February | 1549 (5.58%) | 13.65 (6.69) | −0.18 (−0.66, 0.29) | 0.45 |
| March | 2285 (8.23%) | 14.37 (6.91) | 0.54 (0.11, 0.97) | 0.01 |
| April | 2676 (9.64%) | 16.19 (7.24) | 2.36 (1.95, 2.77) | < 0.0001 |
| May | 2578 (9.28%) | 15.76 (6.80) | 1.93 (1.52, 2.35) | < 0.0001 |
| June | 2505 (9.02%) | 18.98 (7.23) | 5.15 (4.73, 5.56) | < 0.0001 |
| July | 2617 (9.42%) | 20.05 (7.39) | 6.22 (5.81, 6.64) | < 0.0001 |
| August | 2381 (8.57%) | 22.10 (7.97) | 8.27 (7.85, 8.70) | < 0.0001 |
| September | 2276 (8.20%) | 22.45 (8.09) | 8.62 (8.19, 9.05) | < 0.0001 |
| October | 2183 (7.86%) | 20.65 (7.78) | 6.82 (6.38, 7.25) | < 0.0001 |
| November | 2273 (8.19%) | 17.53 (7.27) | 3.70 (3.27, 4.13) | < 0.0001 |
| December | 2284 (8.23%) | 14.79 (6.74) | 0.96 (0.53, 1.39) | < 0.0001 |
| $P$ for trend | < 0.0001 |
| Season of blood collection, N (%) | |
| Spring (March, April and May) | 7539 (27.15%) | 15.49 (7.03) | |
| Summer (June, July and August) | 7503 (27.02%) | 20.34 (7.64) | 4.85 (4.61, 5.09) | < 0.0001 |
| Autumn (September, October and November) | 6732 (24.24%) | 20.20 (7.98) | 4.71 (4.47, 4.95) | < 0.0001 |
| Winter (December, January and February) | 5994 (21.59%) | 14.15 (6.85) | −1.34 (−1.60, −1.09) | < 0.0001 |
| $P$ for trend | < 0.0001 |
by 10 μg/m³ was associated with a 12.4% (OR 1.12; 95% CI 1.07 to 1.18, P-value < 0.00001) increase in the odds for maternal vitamin D deficiency and inadequacy (< 20 ng/mL). In the fully adjusted Model 4, a 10 μg/m³ increase in the PM₁₀ 60-day moving daily average was associated with a 11.3% (OR 1.11; 95% CI 1.07 to 1.15, P-value < 0.00001) increase in the odds of maternal vitamin D deficiency and inadequacy (< 20 ng/mL).

In the subgroup analyses stratified by season, we further investigated the role of season on the association between the maximum cumulative effects of PM and serum 25OHD levels. For PM₂.₅ (Table 3), both linear and nonlinear effect values were higher in summer and autumn and lower in winter and spring (P-values for interaction < 0.001). Figure 3A shows the different nonlinear associations between the 45-day moving daily average PM₂.₅ concentration and maternal serum 25OHD levels stratified by season. In addition, we calculated, using the two-piecewise linear regression model, the turning point of the adjusted smoothed curve. Specifically, the difference between the two slopes was at its maximum in autumn, and the turning point (45-day moving daily average PM₂.₅ concentration) was 31.11 μg/m³. For PM₁₀ (Table 4), linear regression analysis showed a significant interaction for season (interaction P-value < 0.001), but the non-linear model showed this interaction was not significant (interaction P-value = 0.38). Figure 3B shows the different nonlinear associations between the 60-day moving daily average PM₁₀ concentration and maternal serum 25OHD levels stratified by season. It is worth mentioning that, in autumn, the relationship between PM₁₀ and 25OHD levels was nonlinear, and the turning point was 38.10 μg/m³. Specifically, when the 60-day moving daily average PM₁₀ concentration ranged from 32.32 to 38.10 μg/m³, a stronger negative relationship was found between PM₁₀ and serum 25OHD levels (β = −1.12; 95% CI −1.51 to −0.73; P-value < 0.0001; number of pregnant women, 878).

The threshold effect analysis used to examine the associations between maternal age and serum 25OHD levels during the second trimester of pregnancy revealed a stronger positive relationship between age and serum
25OHD levels when the women were 15 to 25 years of age and a weaker positive relationship when they were 25 to 47. The results of four different adjusted models were robust (Fig. S3, Table S4). We then categorized the pregnant women using a threshold of 25 years according to the results of the threshold effect analysis and further investigated the modification effect of age on the association between the maximum cumulative effects of PM and serum 25OHD levels. Table S5 shows that the interaction between age and PM2.5 was not significant (linear interaction $P$-value = 0.08 and non-linear interaction $P$-value = 0.06), while Table S6 shows the interaction between age and PM10 had a marginally significant effect on serum 25OHD levels (linear $P$-value for interaction = 0.045 and non-linear $P$-value for interaction = 0.04).

In the subgroup analyses stratified by meteorological factors, Tables 5 and 6 showed the associations between PM and serum 25OHD levels during the second trimester of pregnancy were generally modified by meteorological factors, although wind speed had no modification effect on PM2.5. Of particular interest, there was a positive association between PM concentration and 25OHD levels under low relative humidity. The result of this stratification was the opposite to the final conclusion.

Discussion

Based on our knowledge of the literature, this epidemiological study is the first to focus on the independent relationship between PM and maternal serum 25OHD levels during the second trimester of pregnancy after adjusting for meteorological factors. We found vitamin D deficiency, inadequacy, and adequacy in 23.5%, 41.3%, and
35.2% of pregnant women during the second trimester of pregnancy, respectively. We found that the maximum cumulative effects of PM2.5 occurred at lag 45 days and the maximum cumulative effects of PM10 occurred at lag 60 days. However, the effect values were drastically reduced after adjusting for temporal and/or meteorological factors. The results indicated that PM has a limited influence on maternal serum 25OHD levels.

The list of studies that have linked VDD to complications of pregnancy continues to grow: vitamin D status has been associated with gestational diabetes36–39, aeroallergen sensitization40, and markers of regulatory immunity41. A meta-analysis of eight studies found a significant association between VDD and the risk of pre-eclampsia, which was more evident in studies that defined VDD as 25OHD < 50 nmol/L and those from the USA42. In addition, a meta-analysis of 24 observational studies confirmed the association between VDD (< 50 nmol/L) and an increased risk of preterm birth (OR 1.58; 95% CI 1.08 to 2.31)43. With respect to birthweight, a meta-analysis of three observational studies found a weak positive association between maternal vitamin D status and birthweight after adjusting for potential confounders44. In addition, recent reviews suggested that appropriate levels of vitamin D during pregnancy are associated with less morbidity during pregnancy45,46.

Zhao et al. reported an association between prenatal exposure to higher PM2.5 and PM10 levels and a decrease in circulating 25OHD concentrations in women in the third trimester and the entire pregnancy24. They reported a 10 μg/m³ increase in PM2.5 and PM10 exposure during the entire pregnancy was associated with a 4.62% (95% Table 3. Threshold effect analysis examining associations between 45-day moving daily average PM2.5 levels and maternal serum 25OHD levels during second trimester in subgroups stratified by season of blood collection. PM2.5 particulate matter with an aerodynamic diameter of ≤ 2.5 μm, 25OHD 25-hydroxy vitamin D, CI confidence interval, LRT logarithmic likelihood ratio test. Adjusted for year, age, 45-day moving daily average atmospheric pressure, sunshine duration, relative humidity and wind speed. *Linear analysis, P-value < 0.05 indicates a linear relationship. aNon-linear analysis. bP < 0.05 means Model B is significantly different from Model A, which indicates a non-linear relationship.

Table 3. Threshold effect analysis examining associations between 45-day moving daily average PM2.5 levels and maternal serum 25OHD levels during second trimester in subgroups stratified by season of blood collection. PM2.5 particulate matter with an aerodynamic diameter of ≤ 2.5 μm, 25OHD 25-hydroxy vitamin D, CI confidence interval, LRT logarithmic likelihood ratio test. Adjusted for year, age, 45-day moving daily average atmospheric pressure, sunshine duration, relative humidity and wind speed. *Linear analysis, P-value < 0.05 indicates a linear relationship. aNon-linear analysis. bP < 0.05 means Model B is significantly different from Model A, which indicates a non-linear relationship.

| Model Aa | Spring | Summer | Autumn | Winter | Total |
|----------|--------|--------|--------|--------|-------|
| One line slope, β (95% CI) P-value | −0.027 (−0.069, 0.014) 0.19 | −0.19 (−0.25, −0.13) < 0.0001 | −0.173 (−0.250, −0.097) < 0.0001 | −0.029 (−0.051, −0.006) 0.01 | −0.032 (−0.046, −0.018) < 0.0001 |
| Model Bb | Turning point (K), μg/m³ | 38.62 | 35.40 | 31.11 | 46.31 | 20.07 |
| < K, β (95% CI) P-value | −0.23 (−0.33, −0.13) < 0.0001 | −0.35 (−0.43, −0.27) < 0.0001 | 0.020 (−0.086, 0.125) 0.71 | −0.130 (−0.192, −0.068) < 0.0001 | −1.80 (−2.07, −1.53) < 0.0001 |
| > K, β (95% CI) P-value | 0.080 (0.016, 0.145) 0.02 | 0.169 (0.038, 0.300) 0.01 | −0.55 (−0.71, −0.39) < 0.0001 | −0.013 (−0.038, 0.011) 0.28 | −0.022 (−0.036, −0.008) 0.002 |

| Slope2–Slope 1, β (95% CI) P-value | 0.31 (0.17, 0.45) < 0.0001 | 0.52 (0.35, 0.69) < 0.0001 | −0.57 (−0.78, −0.36) < 0.0001 | 0.12 (0.05, 0.18) 0.0006 | 1.78 (1.51, 2.04) < 0.0001 |
| Predicted 25OHD levels at K (95% CI), ng/mL | 15.98 (15.65, 16.29) | 18.30 (17.98, 18.63) | 19.47 (19.14, 19.80) | 14.28 (14.02, 14.54) | 20.64 (20.49, 20.78) |
| LRT, P-value | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

Figure 3. Adjusted smoothed curves for 45-day moving daily average PM2.5 concentration (A), 60-day moving daily average PM10 concentration (B), and maternal serum 25OHD levels during pregnancy stratified by seasons. Thresholds were nonlinear associations between PM and 25OHD, as evidenced in generalized additive models. Adjustment factors included year, age, corresponding-day moving daily average atmospheric pressure, sunshine duration, relative humidity, and wind speed. 25OHD 25-hydroxy vitamin D, PM2.5 particulate matter with an aerodynamic diameter of ≤ 2.5 μm, PM10 particulate matter with an aerodynamic diameter of ≤ 10 μm.
Table 4. Threshold effect analysis examining associations between 60-day moving daily average PM$_{10}$ level and maternal serum 25OHD levels during second trimester in subgroups stratified by season of blood collection. Adjusted for year, age, 60-day moving daily average atmospheric pressure, sunshine duration, relative humidity and wind speed. PM$_{10}$ particulate matter with an aerodynamic diameter of ≤ 10 μm, 25OHD 25-hydroxy vitamin D, CI confidence interval, LRT logarithmic likelihood ratio test. *Linear analysis, $P$-value < 0.05 indicates a linear relationship. Non-linear analysis. $P$ < 0.05 means Model B is significantly different from Model A, which indicates a non-linear relationship.

|               | Spring           | Summer          | Autumn          | Winter          | Total          |
|---------------|------------------|-----------------|-----------------|-----------------|---------------|
| One line slope, β (95% CI) |                  |                 |                 |                 |               |
| P-value        |                  |                 |                 |                 |               |
| Turning point (K), μg/m$^3$ | 93.15            | 45.07           | 38.10           | 113.18          | 38.28         |
| P-value        |                  |                 |                 |                 |               |

Table 5. Associations between 45-day moving daily average PM$_{2.5}$ levels and maternal serum 25OHD levels during second trimester of pregnancy in subgroups stratified by meteorological factors. Adjusted for year, season, 45-day moving daily average atmospheric pressure, sunshine duration, relative humidity and wind speed except the subgroup variable. PM$_{2.5}$ particulate matter with an aerodynamic diameter of ≤ 2.5 μm, 25OHD 25-hydroxy vitamin D, CI confidence interval.

|               | N  | β (95% CI) | P-value for interaction |
|---------------|----|------------|-------------------------|
| 45-day moving daily average atmospheric pressure |    |            |                         |
| Tertile 1 (1002.65–1010.69 hPa) | 9247 | −0.19 (−0.25, −0.13) | <0.0001 |
| Tertile 2 (1010.74–1020.73 hPa) | 9260 | −0.042 (−0.077, −0.007) | 0.02 |
| Tertile 3 (1020.75–1028.82 hPa) | 9261 | −0.023 (−0.041, −0.005) | 0.01 |
| 45-day moving daily average relative humidity |    |            |                         |
| Tertile 1 (62.58–71.11%) | 9220 | 0.14 (0.11, 0.18) | <0.0001 |
| Tertile 2 (71.13–77.04%) | 9275 | −0.086 (−0.111, −0.060) | <0.0001 |
| Tertile 3 (77.07–94.33%) | 9273 | −0.14 (−0.17, −0.10) | <0.0001 |
| 45-day moving daily average sunshine duration |    |            |                         |
| Tertile 1 (1.28–4.10 h) | 9136 | −0.044 (−0.064, −0.024) | <0.0001 |
| Tertile 2 (4.12–5.14 h) | 9303 | −0.030 (−0.063, 0.003) | 0.07 |
| Tertile 3 (5.15–8.68 h) | 9329 | −0.019 (−0.024, −0.14) | <0.0001 |
| 45-day moving daily average wind speed |    |            |                         |
| Tertile 1 (1.36–1.87 m/s) | 9138 | −0.068 (−0.088, −0.049) | <0.0001 |
| Tertile 2 (1.88–2.12 m/s) | 9117 | −0.040 (−0.069, −0.011) | 0.07 |
| Tertile 3 (2.13–2.65 m/s) | 9513 | −0.047 (−0.091, −0.004) | 0.03 |

CI 26.31% to 22.93%) and 5.06% (95% CI 26.50% to 23.62%) decrease in 25OHD levels, respectively. In contrast to the analysis they conducted, we first investigated the time window for the largest cumulative effect of PM at the individual level and then adjusted for temporal and meteorological factors. Although both effect sizes of PM$_{2.5}$ and PM$_{10}$ in the fully adjusted models were small (β-value of PM$_{2.5}$ = −0.032; β-value of PM$_{10}$ = −0.039, respectively), they were highly significant ($P$-value < 0.00001). The β-values showed two large drops, one after adjusting for season and the other after adjusting for atmospheric pressure. Due to the collinearity of atmospheric pressure and temperature, it can be inferred that season and atmospheric pressure/temperature may have been important confounders in the regression model. Thus, in some correlation analyses of PM and vitamin D levels, the independent role of PM may have been overestimated when there was no adjustment for meteorological factors. On the other hand, there is now evidence that 25OHD accumulates in skeletal muscle cells, which provide a functional store during the winter months. The mechanism is mediated by the muscle cell uptake of circulating vitamin-D-binding protein (DBP) through a megalin–cubilin membrane transport process. If ways to optimize the efficiency of the muscle conservation mechanism for 25OHD could be found, e.g., a pharmacological agent or some exercise regime, perhaps that optimization would ensure that vitamin D status is also...
PM levels and it is difficult to determine its effect on UV radiation. More recently, PM10 was found to be negatively correlated with the 60-day moving daily average atmospheric pressure. Guan et al. reported that PM levels and surface pressure were analyzed for 366 cities, and peak PM concentrations occurred in winter in most regions, and there were significant correlations between PM levels and precipitation, relative humidity, air temperature, and wind speed. However, other studies that only adjusted for season, our study precisely adjusted for meteorological factor exposure at the individual level.

On the other hand, meteorological factors are also related to periodic changes in PM concentrations. Weather and climate are the most influential factors affecting the chemistry and atmospheric residence time of PM. In a study in China, the geographical and temporal variations in PM levels and coinciding meteorological conditions were analyzed for 366 cities, and peak PM concentrations occurred in winter in most regions, and there were significant correlations between PM levels and precipitation, relative humidity, air temperature, and wind speed. However, other studies that only adjusted for season, our study precisely adjusted for meteorological factor exposure at the individual level.

Indeed, in areas with distinct seasons, 25OHD concentrations in the population fluctuate over time. Many studies showed season to be the primary factor affecting serum 25OHD levels. Periodic changes in the seasons affect periodic changes in meteorological factors, such as temperature, humidity, and sunshine duration. Hence, unlike other studies that only adjusted for season, our study precisely adjusted for meteorological factor exposure at the individual level.

On the other hand, meteorological factors are also related to periodic changes in PM concentrations. Weather and climate are the most influential factors affecting the chemistry and atmospheric residence time of PM. In a study in China, the geographical and temporal variations in PM levels and coinciding meteorological conditions were analyzed for 366 cities, and peak PM concentrations occurred in winter in most regions, and there were significant correlations between PM levels and precipitation, relative humidity, air temperature, and wind speed. However, other studies that only adjusted for season, our study precisely adjusted for meteorological factor exposure at the individual level.

Indeed, in areas with distinct seasons, 25OHD concentrations in the population fluctuate over time. Many studies showed season to be the primary factor affecting serum 25OHD levels. Periodic changes in the seasons affect periodic changes in meteorological factors, such as temperature, humidity, and sunshine duration. Hence, unlike other studies that only adjusted for season, our study precisely adjusted for meteorological factor exposure at the individual level.

Over 90% of the vitamin D in the body is synthesized in human skin after the exposure of precursor 7-dehydrocholesterol to UVB (290–315 nm) radiation from the sun. The strength of the UVB during sun exposure, and therefore the amount of vitamin D synthesized, is affected by solar zenith angle (SZA)—the angle between the local vertical and the sun's position. Hence, the most intense solar radiation occurs when the SZA is small, i.e., which at lower altitudes, is around 11:00–15:00 h in the summer, at which time the synthesis of vitamin D by the skin is most active. At latitudes > 50°, human skin participates in very little vitamin D synthesis during winter and spring for all skin types and ethnicities. In addition, the amount of vitamin D produced is dependent on local weather conditions, such as the percentage cloud cover, which filters UVB radiation, and has an impact in all seasons and hours of the day. Thus, because PM can absorb and diffuse solar irradiation, some scholars have hypothesized that PM can indirectly reduce vitamin D formation by reducing UVB exposure. However, other scholars have argued that there is significant spatiotemporal variation in the morphology, chemical makeup, density of PM, and it is difficult to determine its effect on UV radiation. More recently, PM10 was found to be a significant negative predictor of solar UVB radiation, but the effect of PM10 was minuscule. This conclusion can be used to further deduce that PM10 has an effect on vitamin D levels, but the effect is small, which is consistent with the results of our study. Combined with the above views, we propose a hypothesis (see Fig. S4) that PM and meteorological factors indirectly influence the cyclical changes of vitamin D in pregnant women by impacting the level of personal UVB exposure. For example, in winter, when the temperature is lower and there are fewer hours of sunshine, the PM concentration is higher, but pregnant women spend less time outdoors and wear more clothes, which lead to lower solar UVB radiation exposure, reducing the synthesis of vitamin D.

Table 6. Associations between 60-day moving daily average PM10 levels and maternal serum 25OHD levels during second trimester of pregnancy in subgroups stratified by meteorological factors. Adjusted for year, season, 60-day moving daily average atmospheric pressure, sunshine duration, relative humidity and wind speed except the subgroup variable. PM10 Particulate matter with an aerodynamic diameter of ≤ 10 μm, 25OHD 25-hydroxy vitamin D, CI confidence interval.

| Subgroup                              | N     | β (95% CI)          | P-value | P-value for interaction |
|---------------------------------------|-------|---------------------|---------|-------------------------|
| 60-day moving daily average atmospheric pressure |       |                     |         |                         |
| Tertile 1 (1003.24–1010.76 hPa)       | 9241  | −0.15 (−0.19, −0.12) | <0.0001 |                         |
| Tertile 2 (1010.78–1020.92 hPa)       | 9270  | −0.13 (−0.16, −0.11) | <0.0001 |                         |
| Tertile 3 (1020.97–1028.09 hPa)       | 9257  | −0.021 (−0.037, −0.005) | 0.01     |                         |
| 60-day moving daily average relative humidity |       |                     |         |                         |
| Tertile 1 (63.32–71.30%)              | 9189  | 0.071 (0.044, 0.099)  | <0.0001 |                         |
| Tertile 2 (71.32–77.18%)              | 9289  | −0.053 (−0.071, −0.035) | <0.0001 |                         |
| Tertile 3 (77.23–92.27%)              | 9290  | −0.074 (−0.096, −0.051) | <0.0001 |                         |
| 60-day moving daily average sunshine duration |       |                     |         |                         |
| Tertile 1 (1.84–4.07 h)               | 9237  | −0.026 (−0.043, −0.008) | 0.003    |                         |
| Tertile 2 (4.08–5.15 h)               | 9234  | −0.057 (−0.078, −0.035) | <0.0001 |                         |
| Tertile 3 (5.16–7.90 h)               | 9297  | −0.128 (−0.157, −0.099) | <0.0001 |                         |
| 60-day moving daily average wind speed |       |                     |         |                         |
| Tertile 1 (1.34–1.89 m/s)             | 8993  | −0.043 (−0.059, −0.027) | <0.0001 |                         |
| Tertile 2 (1.90–2.11 m/s)             | 9306  | −0.078 (−0.102, −0.054) | <0.0001 |                         |
| Tertile 3 (2.12–2.58 m/s)             | 9469  | −0.094 (−0.124, −0.065) | <0.0001 |                         |
In the subgroup analysis, with the exception of the low relative humidity, a negative effect between PM and 25OHD was evident in all subgroups considered and after careful adjustments. In the interaction analysis, season and most meteorological factors interacted with the association between PM and 25OHD. However, the mechanisms of their interactions were unclear and need to be further investigated in the future.

There were some limitations regarding our study. First, our results were obtained from a Chinese population of pregnant women during the second trimester and cannot be extrapolated to other populations. Second, the study was an analytical retrospective study and hence provides limited evidence that PM exposure and vitamin D outcomes were related, and the difference between cause and effect is uncertain. Third, demographic information was lacking (education level, vitamin D/calcium supplement use, outdoor activities, use of sun protection, and BMI, etc.) for the individuals whose test results were used. However, valuable insights can be gleaned from the study, as it involved the retrospective analysis of a large dataset from a prenatal examination population. We used precise adjustments at the individual level to reveal whether PM levels are independent variables associated with 25OHD concentration. In the future, a more informative vitamin D database will be established, and vitamin D supplementation will be studied. Fourth, solar UVB dose information was not studied; thus, this important indicator could be included in the future studies.

Conclusions

Our study showed there was a small, independent, negative association between PM in the atmosphere and maternal serum 25OHD levels during the second trimester of pregnancy after adjusting for temporal and/or meteorological factors, which indicates that PM may have a limited influence on maternal serum 25OHD levels. Besides taking vitamin D supplements, pregnant women should keep participating in outdoor activities while taking PM protection measures to improve their vitamin D levels when PM levels are high in winter and spring.

Data availability

All data generated or analysed during this study are included in this published article and its Supplementary Information files.

Received: 15 March 2022; Accepted: 27 September 2022
Published online: 07 October 2022

References

1. Holick, M. F. Vitamin D: Evolutionary, physiological and health perspectives. Curr. Drug Targets 12(1), 4–18. https://doi.org/10.2174/13894501179391635 (2011).
2. Hatun, S. et al. Vitamin D deficiency in early infancy. J. Nutr. 135(2), 279–282. https://doi.org/10.1093/jn/135.2.279 (2005).
3. Achkar, M. et al. Vitamin D status in early pregnancy and risk of preeclampsia. Am. J. Obstet. Gynecol. 212(4), 511–517. https://doi.org/10.1016/j.ajo.2014.11.009 (2015).
4. Arnold, D. L. et al. Early pregnancy maternal vitamin D concentrations and risk of gestational diabetes mellitus. Paediatr. Perinat. Epidemiol. 29(3), 200–210. https://doi.org/10.1111/ppe.12188 (2015).
5. Wang, H., Xiao, Y., Zhang, L. & Gao, Q. Maternal early pregnancy vitamin D status in relation to low birth weight and small-for-gestational-age offspring. J. Steroid Biochem. Mol. Biol. 175, 146–150. https://doi.org/10.1016/j.jsbmb.2017.09.010 (2018).
6. Murthi, P. et al. Maternal 25-hydroxyvitamin D is inversely correlated with foetal serotonin. Clin. Endocrinol. (Oxf.) 86(3), 401–409. https://doi.org/10.1111/cen.13281 (2017).
7. Meems, L. M. et al. Parental vitamin D deficiency during pregnancy is associated with increased blood pressure in offspring via Panx1 hypermethylation. Am. J. Physiol. Heart Circ. Physiol. 311(6), H1459–H1469. https://doi.org/10.1152/ajpheart.00141.2016 (2016).
8. Weinert, L. S. & Silveiro, S. P. Maternal-fetal impact of vitamin D deficiency: A critical review. Matern. Child Health J. 19(1), 94–101. https://doi.org/10.1007/s11858-014-0149-7 (2015).
9. Viljakainen, H. T. et al. Maternal vitamin D status determines bone variables in the newborn. J. Clin. Endocrinol. Metab. 95(4), 1749–1757. https://doi.org/10.1210/jc.2009-1391 (2010).
10. Ginde, A. A., Sullivan, A. F., Mansbach, J. M. & Camargo, C. A. Jr. Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. Am. J. Obstet. Gynecol. 202(5), 436–438. https://doi.org/10.1016/j.ajo.2009.11.036 (2010).
11. McAree, T. et al. Vitamin D deficiency in pregnancy—Still a public health issue. Matern. Child Nutr. 9(1), 23–30. https://doi.org/10.1111/mcn.12014 (2013).
12. Vijayendra Chary, A. et al. Vitamin D deficiency in pregnant women impairs regulatory T cell function. J. Steroid Biochem. Mol. Biol. 147, 48–55. https://doi.org/10.1016/j.jsbmb.2014.11.020 (2015).
13. Song, S. J. et al. The high prevalence of vitamin D deficiency and its related maternal factors in pregnant women in Beijing. PLoS ONE 8(12), e85081. https://doi.org/10.1371/journal.pone.0085081 (2013).
14. Bodnar, L. M., Catov, J. M., Roberts, J. M. & Simhan, H. N. Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. J. Nutr. 137(11), 2437–2442. https://doi.org/10.1093/jn/137.11.2437 (2007).
15. Bodnar, L. M. et al. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J. Nutr. 137(2), 447–452. https://doi.org/10.1093/jn/137.2.447 (2007).
16. Brenbeck, P., Winkvist, A. & Olausson, H. Determinants of vitamin D status in pregnant fair-skinned women in Sweden. Br. J. Nutr. 110(5), 856–864. https://doi.org/10.1017/s0007114512005855 (2013).
17. Jensen, C. B. et al. Sources and determinants of vitamin D intake in Danish pregnant women. Nutrients 4(4), 259–272. https://doi.org/10.3390/nu4040259 (2012).
18. Richard, A., Rohrmann, S. & Quack Lötcher, K. C. Prevalence of vitamin D deficiency and its associations with skin color in pregnant women in the first trimester in a sample from Switzerland. Nutrients 9(3), 9030260. https://doi.org/10.3390/nu9030260 (2017).
19. Sowah, D., Fan, X., Dennett, L., Hagvedt, R. & Straube, S. Vitamin D levels and deficiency with different occupations: A systematic review. BMC Public Health 17(1), 519. https://doi.org/10.1186/s12889-017-4436-z (2017).
20. Agarwal, K. S. et al. The impact of atmospheric pollution on vitamin D status of infants and toddlers in Delhi, India. Arch. Dis. Child. 97(2), 111–113. https://doi.org/10.1136/adc.87.2.111 (2002).
21. Kelishadi, R. et al. Independent association between air pollutants and vitamin D deficiency in young children in Isfahan. Iran. Pediatr. Int. Child Health 34(1), 50–55. https://doi.org/10.11179/2046905513y0000000080 (2014).

https://doi.org/10.1038/s41598-022-21383-1
61. Webb, A. R. Who, what, where and when-influences on cutaneous vitamin D synthesis. *Prog. Biophys. Mol. Biol.* **92**(1), 17-25. https://doi.org/10.1016/j.pbiomolbio.2006.02.004 (2006).

62. Webb, A. R., Kline, L. & Holick, M. F. Influence of season and latitude on the cutaneous synthesis of vitamin D3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J. Clin. Endocrinol. Metab.* **67**(2), 373-378. https://doi.org/10.1210/jcem-67-2-373 (1988).

63. Zegarska, B. et al. Air pollution, UV irradiation and skin carcinogenesis: What we know, where we stand and what is likely to happen in the future? *Postepy Dermatol. Allergol.* **34**(1), 6-14. https://doi.org/10.5114/ada.2017.65616 (2017).

**Author contributions**

K.L. contributed to the study conception and design. Y.G., Y.X., X.W., L.C. and S.Y. contributed to the acquisition of data. K.L. and Y.G. contributed to the analysis and interpretation of data. C.L. drafted the manuscript, R.L. and K.L. revised it. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

**Funding**

The study was supported by National Natural Science Foundation of China (CN) (82172441), Elderly Health Research Project of Jiangsu Province (CN) (LKZ2022020), Suzhou Collaborative Innovation Research Project of Medical and Industrial Integration (CN) (SLJ2022023), Clinical Medical Science and Technology Development Fund of Jiangsu University (CN) (JLY2021048) and Suzhou Key Clinical Diagnosis and Treatment Technology Project (CN) (LCZX202024).

**Competing interests**

The authors declare no competing interests.

**Additional information**

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-21383-1.

**Correspondence** and requests for materials should be addressed to K.L.

**Reprints and permissions information** is available at www.nature.com/reprints.

**Publisher’s note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© The Author(s) 2022