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Effect of $PM_{2.5}$ exposure on Vitamin D status among pregnant women: A distributed lag analysis

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ABSTRACT

Background: Serum vitamin D levels are associated with exposure to air pollution, however, the lagged effect of exposure to air pollution remains unknown in pregnant women.
Methods: Pregnant women who delivered at a maternity center in Shanghai, China, from 2015 to 2019 were included in the present study. The concentration of particulate matter 2.5 ($PM_{2.5}$) before 25-Hydroxyvitamin D [25(OH)D] detection was estimated using the satellite-based grid models. The distributed lag non-linear models were performed to examine the lagged association between weekly-specific $PM_{2.5}$ exposure and vitamin D deficiency (VDD) or serum 25(OH)D levels.
Results: Among the 58,025 pregnant women included in the study (mean age at conception, 30.77 ± 3.75 years; mean prepregnancy BMI, 21.09 ± 2.55 kg/m^2), 61.32% were diagnosed with VDD. Weekly-specific $PM_{2.5}$ exposure at weeks 1–10 before the detection of 25(OH)D was significantly associated with an increased incidence of VDD ($p < 0.05$). For every 10 μg/m^3 increase in $PM_{2.5}$ exposure, the serum 25(OH)D level decreased by 1.346 nmol/L (95%CI: 1.183–1.508 nmol/L). The association between average $PM_{2.5}$ exposure and VDD at 1–10 weeks was more significant in weather conditions with low mean sunshine hours (OR: 1.246, 95%CI: 1.221–1.271).
Conclusion: Our study provided suggestive evidence that $PM_{2.5}$ exposure at 1–10 weeks before the 25(OH)D detection may decrease the circulating 25(OH)D levels in pregnant women and increase VDD risk in pregnant women. More attention should be paid to the long-term impact of $PM_{2.5}$, in particular, during weather conditions with a relatively short duration of sunshine.

1. Introduction

Globally, vitamin D deficiency (VDD) is currently a major health problem requiring urgent social attention (Autier et al., 2014; Lips, 2010). Owing to the increasing demand for vitamin D and the further reduction in outdoor activities, pregnant women have a potentially higher risk of experiencing VDD than men and non-pregnant women (Palacios and Gonzalez, 2014). Approximately, 46–87% of pregnant women reportedly have VDD worldwide, especially in Southeast Asia (Saraf et al., 2016). Sufficient vitamin D is vital to support pregnancy and healthy fetal development (Hatun et al., 2005). Emerging evidence suggests that maternal VDD may increase the risk of several adverse outcomes, related to the mother and offspring, including diabetes (Arnold et al., 2015; Yin et al., 2020), preeclampsia (Benachi et al., 2020; Chao-Yan et al., 2021), small for gestational age (SGA) infant (Chen et al., 2017), impaired fetal neurocognitive development (Murthi

Abbreviations: 25OHD, 25-Hydroxyvitamin D; $PM_{2.5}$, particulate matter ≤ 2.5 μg in diameter; BMI, body mass index; DLNMs, distributed lag non-linear models; VDD, vitamin D deficiency.

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et al., 2017), low birth weight (Wang et al., 2018), placental inflammation (Chen et al., 2020; Zhang et al., 2019a), and neonatal infections (Workneh et al., 2021). Therefore, it is imperative to pay additional attention to VDD during gestation.

Maternal vitamin D levels depend on myriad factors, including the race of the mother, geographical location, education level, gestation period, prepregnancy body mass index (BMI), sunlight, vitamin D supplements, sunscreen use, and outdoor activities (Dror et al., 2011; Pratumvinit et al., 2015; Shiraishi et al., 2014). Furthermore, ambient pollutants exposure may reportedly affect the status of 25-Hydroxylvitamin D [25(OH) D] in circulation, — a key biomarker of human vitamin D levels (Hoseinzadeh et al., 2018a). According to several cross-sectional studies, exposure to air pollution in infants (Agarwal et al., 2002), young children (Kelishadi et al., 2014), adolescents (Feizabad et al., 2017a), and women (Hosseinpanah et al., 2010a; Zhao et al., 2019a) was negatively associated with circulating 25(OH)D levels. In a study performed in the Jiangsu province of China, exposure to air particulate pollution during late pregnancy showed a negative correlation with maternal vitamin D concentration (Zhao et al., 2019a). However, there is a paucity of information on the lagged and cumulative effects of ambient particulate matter exposure on plasma vitamin D levels.

Therefore, the present retrospective study, including 58,025 pregnant women in Shanghai, China, was conducted to investigate the association between ambient particulate matter 2.5 ($PM_{2.5}$) exposure and serum vitamin D levels, and then, the lagged effect of ambient $PM_{2.5}$ exposure on vitamin D and its sensitivity in different populations were analyzed using the distributed lag non-linear models (DLNMs).

2. Methods

2.1. Study population

Pregnant women who were examined between January 1, 2015, and December 31, 2019, at the International Peace Maternity and Child Health Hospital (IPMCH) affiliated to Shanghai Jiao Tong University School of Medicine, were included in the present study. The pregnant women were registered during their initial prenatal visit. The inclusion criteria for participants were pregnant women with residential addresses in Shanghai. Pregnancy age at conception, prepregnancy BMI, ward type, parity, gravidity, education level, current residential address, smoking, drinking, disease history, vitamin D supplementation, and other parameters, were collected and recorded in the Hospital Information System (HIS) by trained doctors at the first antenatal clinic visit (gestational period, 9–13 weeks). Among the initial cohort of 76,689 pregnant women, those without information related to 25(OH)D detection and residential address were excluded, and 58,025 participants were finally enrolled in the study (Fig. S1). The protocol of this study was reviewed by the Ethics Committee of IPMCH (No. GKLW 2013–51).

2.2. Exposures

$PM_{2.5}$ data were obtained from near real-time Tracking Air Pollution in China (http://tapdata.org.cn/, TAP) (Geng et al., 2021; Xiao et al., 2021). The TAP database used a two-level machine learning model, combined with synthetic minority oversampling technology and a tree-based gap-filling method. The level of $PM_{2.5}$ at 10 x 10 km spatial resolution was estimated using information from multiple data sources, such as $PM_{2.5}$ monitoring data, satellite remote sensing aerosol optical depth (AOD) data, operational Community Multiscale Air Quality (CMAQ) simulation, meteorological reanalysis, land use data, altitude, and population. The first stage model predicted high pollution events and resamples the model training data using the Synthetic Minority Oversampling Technique (SMOTE) algorithm. This algorithm balances the ratio of high pollution events to normal events in the model training dataset (Geng et al., 2021). High pollution events were predicted by the first-stage random forest model trained with the resampled data In the second-stage model, the residuals between $PM_{2.5}$ concentrations simulated by CMAQ and $PM_{2.5}$ observed concentrations are used to build a second random forest model, and replacing $PM_{2.5}$ observed concentrations with residuals as the learning target values can enhance the response of each parameter to $PM_{2.5}$ concentration changes and improve the accuracy of the simulation (Geng et al., 2021). The decision tree-based modeling algorithm fills the gap in satellite retrieval. The average cross-validation R^2 of the model in different years was 0.83. All the residential addresses were geocoded and the daily and weekly $PM_{2.5}$ exposure levels of each address were assigned from the model. Daily meteorological data from 2013 to 2020 and sunshine duration were obtained from the publicly accessible China National Meteorological data sharing system.

2.3. Maternal plasma 25(OH)D measurement

Fasting blood samples of pregnant women were obtained at the first prenatal examination (gestational period, 9–13 weeks), then the serum was obtained by centrifugation and stored in a − 20 °C refrigerator until analysis (Zhang et al., 2019b). Serum concentrations of 25(OH)D were measured by chemiluminescence particle immunoassay on an architect I2000SR automatic analyzer (Abbott diagnostics), and two qualified inspectors drew the standard curve according to standard clinical procedures. The detection range was 2.00–400.00 nmol/L. According to the international general standards, maternal VDD was considered as a concentration of 25(OH)D in serum < 50.00 nmol/L (Dror and Allen, 2010; Lawlor et al., 2013).

2.4. Statistical methods

The mean weekly-specific residential $PM_{2.5}$ exposure and sunshine duration before 25(OH)D detection was calculated. Week 0 is defined as the 7 days before the serum 25(OH)D detection (including the detection day). The distribution of weekly-specific $PM_{2.5}$ concentration, weekly-specific sunshine duration, and serum 25(OH)D level was presented as a percentile, density graph, and mean ± SD, respectively.

DLNMs (Gasparrini, 2011) were applied to evaluate the lag influence of weekly-specific $PM_{2.5}$ and sunshine duration on 25(OH)D levels and VDD. DLNMs can flexibly simulate the exposure level and adjust the delayed effect to establish the relationship between exposure-response and delayed response in one model (Gasparrini, 2014). Several health effects of pollutants on pregnant women can be evaluated using this approach (Neven et al., 2021; Yang et al., 2021). The maximum lag was approximately 19 weeks when considering the Akaike information criterion (AIC). The weekly-specific risk of VDD for an increment of 10 $\mu g/m^3$ in $PM_{2.5}$, or 1 h in sunshine duration was reported as an odds ratio (OR) with a 95% confidence interval (95% CI) based on DLNMs. Weekly-specific estimates (levels and ORs) were reported with 95% CI of DLNM-based associations as the difference of 25(OH)D. Similarly, the DLNM package was used to calculate cumulative weekly specific associations, that is, predictions from exposure duration to lag L to 0, which can be achieved by calculating the sum of lag-specific contributions (Gasparrini, 2011).

The sunshine duration was categorized as long or short sunshine periods based on the median (4.43 h). Subsequently, $PM_{2.5}$ concentrations and sunshine of specific lag weeks (1–10 weeks) with significant statistical differences were averaged and stratified according to the duration of the sunshine to analyze the potential interaction. The effects of $PM_{2.5}$ exposure on VDD and serum levels of 25(OH)D in each specific week were also analyzed after adjusting for the sunshine duration. Heat maps were used to intuitively demonstrate the interaction between $PM_{2.5}$ exposure and sunshine duration of continuous variables of VDD and serum 25(OH)D.

Stratification analysis was conducted to examine the air pollution effect on pregnant women with different characteristics, and the

stratification factors used were as follows: gestational age (<35 or ≥35 years), prepregnancy BMI (<24 or ≥ 24 kg/m^2), and vitamin D supplementation (yes or no). In the sensitivity analysis, the classification criteria for 25(OH)D was changed to < 25 nmol/L, and the DLNM model was conducted again to check the stability of the results. To exclude the effects of nephritis and thyroid disease on the results, the effect of a specific week of $PM_{2.5}$ exposure on VDD was analyzed after excluding pregnant women with previous nephritis (n = 121) and thyroid disease (n = 2454).

All the analyses were conducted using R (Version: 4.0.1), and the two-sided test with p-values < 0.05 was considered statistically significant.

3. Results

3.1. Population characteristics

Participant characteristics are presented in Table 1. The mean age at conception was 30.77 ± 3.75 years, the mean prepregnancy BMI was 21.09 ± 2.55 kg/m^2, 0.34% of women were reported smoking during pregnancy, 0.89% was reported drinking during pregnancy, 71.43% were primipara, and 15.86% received vitamin D supplementation before 25(OH)D detection. The serum 25(OH)D concentration at 9–13 weeks was 45.91 ± 17.58 nmol/L, and the incidence of VDD (< 50 nmol/L) was 61.32%.

The average weekly-specific $PM_{2.5}$ exposure was 42.89 ± 18.96 μg/m^3 and the average weekly daily sunlight was 4.60 ± 2.39 h during the gestational week in which vitamin D was detected (Fig. 1 and Table S1). The median (25th–75th percentile) ambient weekly-specific $PM_{2.5}$ and sunshine exposures during the week of detection were 39.57 μg/m^3 (29.00 – 53.43 μg/m^3) and 4.43 h (2.84 – 6.40 h), respectively.

Table 1
Population characteristics of the pregnant woman.

Characteristics	Pregnancy women
BMI, mean (SD), kg/m^2	21.09(2.55)
Pregnant age, mean (SD), years	30.77(3.76)
Serum 25(OH)D, mean (SD), nmol/L	45.91(17.58)
Gravidity, n (%)	
0	30,090(51.86)
1	16,657(28.71)
> 1	11,274(19.43)
Detection season, n (%)	
Spring	14,999(25.85)
Summer	14,513(20.01)
Autumn	14,183(22.44)
Winter	14,330(24.70)
Education level	
High school and below	2902(5.02)
Collage	42,784(74.00)
Postgraduate and above	12,130(20.98)
Parity, n (%)	
1	41,448(71.43)
> 1	16,577(28.57)
Ward type, n (%)	
General ward	52,508(90.49)
Senior ward	5517(9.51)
Insurance type, n (%)	
No	49,642(85.55)
Yes	8383(14.45)
Drinking, n (%)	
No	57,506(99.11)
Yes	519(0.89)
Smoking, n (%)	
No	57,825(99.66)
Yes	200(0.34)
Vitamin D supplement, n (%)	
No	48,822(84.14)
Yes	9203(15.86)
VDD, n (%)	
No	22,442(38.68)
Yes	35,583(61.32)

3.2. Association between weekly-specific $PM_{2.5}$ or sunshine duration and VDD or serum 25(OH)D level

Mean weekly-specific residential $PM_{2.5}$ exposure levels were used to analyze the lag effect on VDD. As shown in Fig. 2 A, weekly-specific $PM_{2.5}$ exposure during 1–10 weeks before 25(OH)D detection increased the risk of VDD. The highest risk of VDD (OR: 1.027, 95% CI: 1.022 − 1.033) was observed with every 10-μg/m^3 increase in weekly-specific $PM_{2.5}$ exposure in the 4th week before 25(OH)D detection. The results of several adjustment models were similar. Weekly-specific $PM_{2.5}$ exposure significantly reduced 25(OH)D levels 1–10 weeks before the detection, and the highest reduction of 25(OH)D levels (−0.281, 95% CI: −0.235 to 0.327 nmol/L) was observed with every-10 μg/m^3 increase in weekly-specific $PM_{2.5}$ exposure lags of 4 weeks (Fig. S4A). Increasing the sunshine time from 0 to 19 weeks before 25 (OH)D detection significantly reduced the ORs of VDD (Fig. 2B) and increased the serum 25(OH)D level (Fig. S4B). As shown in Fig. S3 and S5, the association between $PM_{2.5}$ exposure in the specific week and VDD and serum 25(OH)D level was similar to that before adjustment.

The exposure-response curves of cumulative weekly-specific residential $PM_{2.5}$ and sunshine time are presented in Fig. 3A. The negative cumulative difference of 25(OH)D was associated with weekly-specific $PM_{2.5}$ exposure. As shown in Fig. S6A, the positive cumulative OR of VDD was associated with weekly-specific $PM_{2.5}$ exposure. The incidence of VDD showed a tendency to increase (Fig. 3A) and serum 25(OH)D levels tended to decrease (Fig. S6A) with the increase in ambient $PM_{2.5}$ exposure in pregnant women. With every 10-μg/m^3 increase in $PM_{2.5}$ exposure, there was an association with a decrease of 1.346 nmol/L (95% CI: 1.183 – 1.508 nmol/L) in serum 25(OH)D levels. Positive cumulative differences of 25(OH)D levels were associated with weekly-specific sunshine duration. The OR of VDD accumulation was negatively correlated with sunshine duration (Fig. S6B).

3.3. Relationship between $PM_{2.5}$ exposure and sunshine duration and VDD or serum 25(OH)D level

Mean values of $PM_{2.5}$ exposure and duration of sunshine hours for the specific weeks (weeks 1–10) with significant differences (Fig. 2) were calculated. The incidence of VDD for a 10-μg/m^3 increase in average $PM_{2.5}$ exposure for weeks 1–10 was stratified based on whether or not the duration of sunshine was greater than the median (Fig. 1). As shown in Fig. 4 A, the association between 10-week average $PM_{2.5}$ exposure and VDD prevalence was greater in the weather with low mean sunshine duration (OR: 1.246, 95% CI: 1.221 – 1.271). The association between weekly-specific $PM_{2.5}$ exposure and VDD prevalence was analyzed based on the stratification described above. The effect of $PM_{2.5}$ exposure in 1–8 weeks before serum 25(OH)D detection was increased considerably in weather with fewer daylight hours (Fig. 4B). Heatmaps showed that as the average $PM_{2.5}$ exposure level increased 1–9 weeks before detection, the effect was more robust in weather conditions with fewer daylight hours and the interaction term was statistically significant (p < 0.001) (Figs. 4B and S7).

3.4. Stratification analysis

We conducted the stratified analysis using the DLNM models by gestational age (<35 vs. ≥35 years), prepregnancy BMI (<24 vs. ≥24 kg/m^2), and vitamin D supplementation (yes/no). Women with a high prepregnancy BMI had a higher risk of VDD prevalence for each 10-μg/m^3 increase in $PM_{2.5}$ exposure (3–6 weeks before 25(OH)D detection) compared to those with low prepregnancy BMI (Fig. 5).

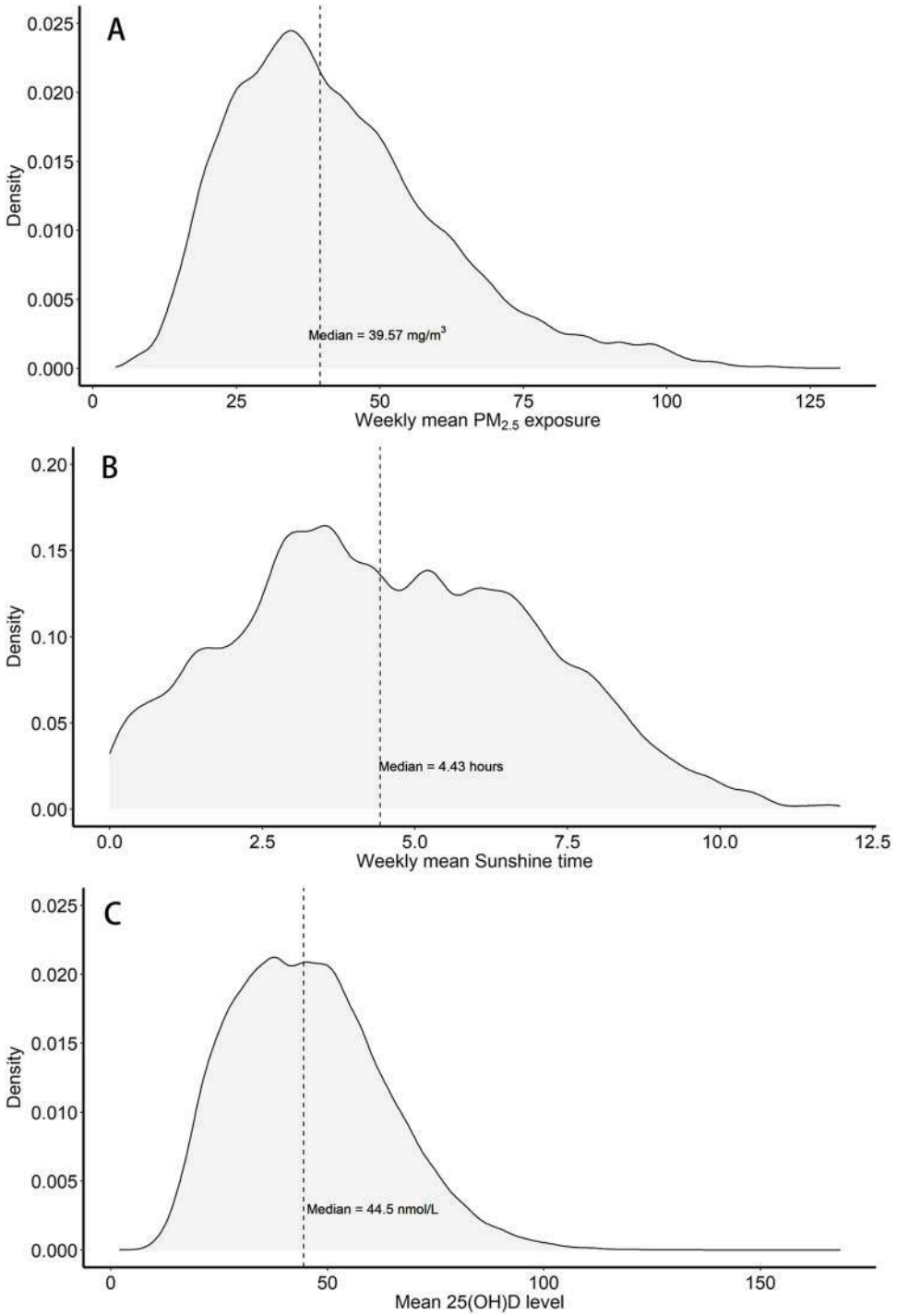

Fig. 1. The distribution of mean weekly $PM_{2.5}$ exposures (A), sunshine time (B), and serum 25(OH)D level (C) during the gestational week where vitamin D was detected. Each woman was detected for vitamin D levels at 9–13 weeks of gestation.

3.5. Sensitivity analysis

In the sensitivity analysis, the diagnostic threshold for VDD was changed to < 25 nmol/L, and the results showed that weekly-specific $PM_{2.5}$ exposure 3–8 weeks before 25(OH)D detection was associated with the incidence of VDD, and the highest effect was observed at the 5-week lag (OR: 1.015, 95% CI: 1.007–1.023) (Fig. S10). However, after adjusting the model for weekly-specific daylight hours, weekly-specific $PM_{2.5}$ exposure 3–6 weeks before 25(OH)D detection was associated with VDD. After excluding pregnant women with a history of nephritis and thyroid disease, the ORs and cumulative ORs of VDD were similar to those of non-exclusion for weekly-specific $PM_{2.5}$ exposure.

4. Discussion

Results of the present retrospective study showed that a higher $PM_{2.5}$ exposure in early pregnancy was associated with a lower level of maternal circulating 25(OH)D, and a higher risk of maternal VDD. By using the DLNM models, it was evident that $PM_{2.5}$ exposure showed a lagged effect, and $PM_{2.5}$ exposure 1–10 weeks before 25(OH)D detection increased the risk of VDD and reduced maternal circulating 25(OH)D concentration. Furthermore, the results suggested that the effect of

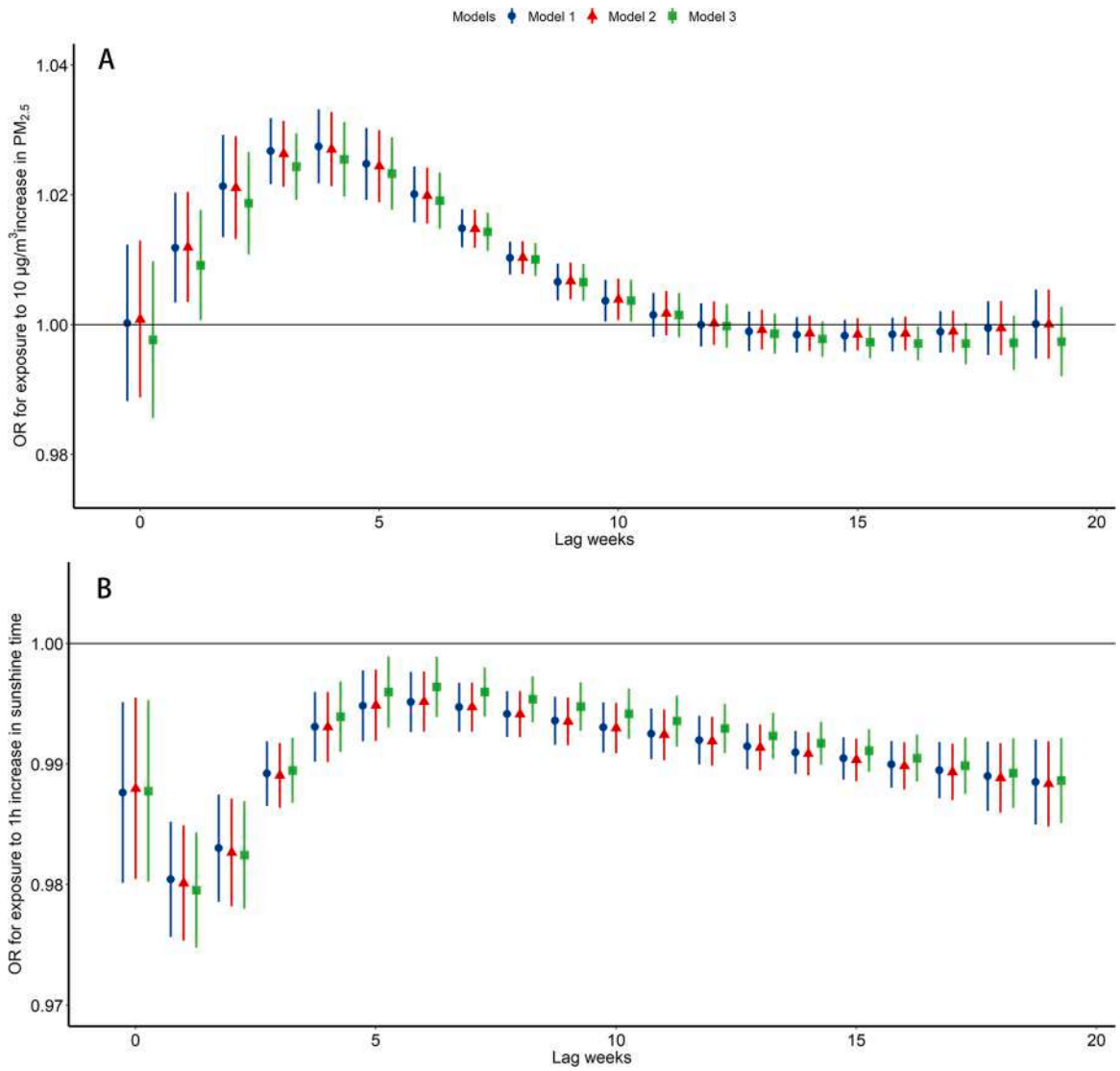

Fig. 2. Odds ratios of VDD in association with weekly-specific prenatal exposure to $PM_{2.5}$ (A), and Sunshine time (B) during and before pregnancy. Model 1 adjusted for pregnant age, parity, gravidity, education level, insurance type, number of fetuses, detected season, smoking, and drinking; Model 2 adjusted for in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Model 3 adjusted for in addition to the confounders in adjusted model 2, Vitamin D supplement (Yes/No) was also adjusted.

$PM_{2.5}$ exposure was more robust in terms of weather conditions with a short sunshine duration.

The findings of the present study were consistent with those of several previous studies that had examined the influence of air pollution on vitamin D status in adolescents (Feizabad et al., 2017b), healthy women (Hosseinpanah et al., 2010b), and pregnant women (Zhao et al., 2019b). However, these studies used urban air pollution concentrations instead of assessing individual air pollution exposure levels. Moreover, studies analyzing the lag effect of weekly-specific air pollution on vitamin D levels are scarce.

Our study found that maternal exposure to $PM_{2.5}$ for 1–10 weeks (7–77 days) of the lag increased the risk of VDD and decreased serum 25 (OH)D concentrations. These findings are similar to the results of a previous study conducted in Jiangsu, China (Zhao et al., 2019b), which reported that $PM_{2.5}$ exposure in the second trimester was associated with a decrease in serum 25(OH)D concentration; however, it showed no significant association with the risk of VDD. The longest lag time (77 days) of $PM_{2.5}$ exposure for serum 25(OH)D concentration observed in the present study was greater than the 15-days of the half-life of human $25(OH)D_3$ (Jones, 2008). However, this lag time was similar to the half-life of systemic vitamin D. Experimental studies revealed that the whole-body half-life of vitamin D was approximately 60–82 days (Cipriani et al., 2013a, 2013b; Mawer et al., 1971). A study in the United States in 2013 reported a half-life of 74 days following a one-time injection of 600,000 IU of vitamin D. In an interventional study in 2015, subjects received 100,000 IU of vitamin D, followed by a 4800 IU daily supplement of vitamin D, and found that the half-life of vitamin D was 82 days (Oliveri et al., 2015). $PM_{2.5}$ exposure may cause inflammatory reactions in humans (Chu et al., 2019; Feng et al., 2016), and such inflammatory reactions consume substantial amounts of vitamin D, thereby indicating that they may be a potential cause of VDD. People with severe inflammation have a shorter vitamin D half-life (about 10 days) (Bang et al., 2011), and the sustained inflammatory reactions caused by $PM_{2.5}$ exposure and the depletion of vitamin D by the inflammatory response may influence the lag time of the effect of $PM_{2.5}$ exposure on vitamin D.

The mechanism underlying the process through which air pollution reduces circulating 25(OH)D levels requires further elucidation. It has been found that $PM_{2.5}$ absorbs solar radiation, thus decreasing the quantity of ultraviolet-B (UV-B) reaching the Earth's surface (Barnard

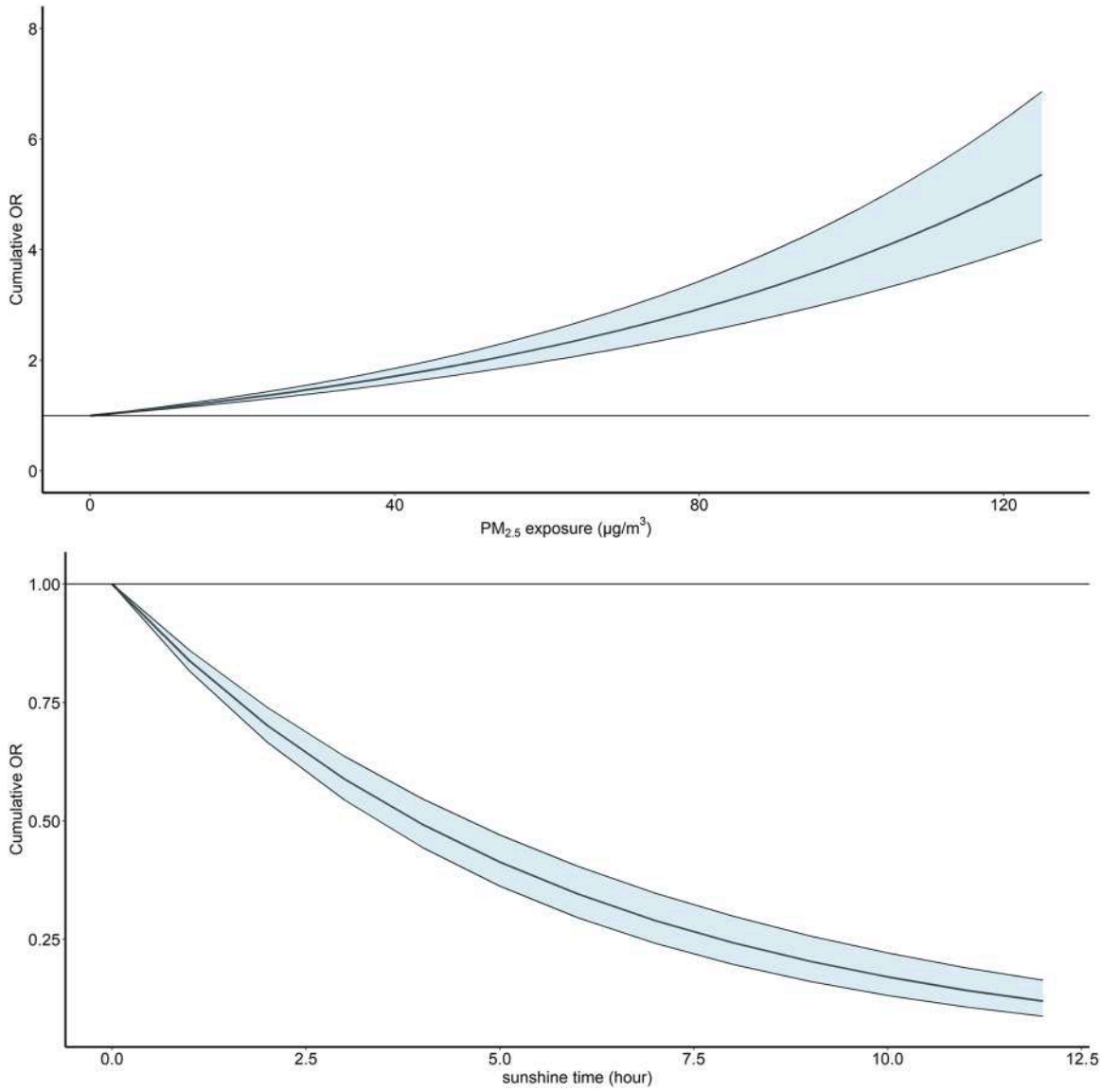

Fig. 3. The cumulative exposure-response curves of odds ratio (VDD) in association with weekly-specific exposure to $PM_{2.5}$ (A), and Sunshine time (B) during and before pregnancy. Model adjusted for pregnant age, parity, gravidity, education level, insurance type, number of fetuses, detected season, pre-pregnancy BMI, Vitamin D supplement, smoking, and drinking.

et al., 2003). Since sunlight contributes more than 90% of human vitamin D production (Hoseinzadeh et al., 2018b), studies have demonstrated that particulate air pollution reduces 25(OH)D status by mediating a reduction in the amount of solar UV-B radiation reaching the ground (Zhao et al., 2019b). Our study found that the impact of $PM_{2.5}$ exposure on VDD was significant in weather conditions with a shorter duration of sunshine. This may be attributable to the fact that an increase in ambient $PM_{2.5}$ concentration reduces the amount of solar UV radiation reaching the Earth's surface, especially in weather conditions with relatively shorter durations of sunshine. Although ambient $PM_{2.5}$ can reduce the amount of UV radiation on the Earth's surface under conditions of longer sunshine duration, it can still ensure enough UV radiation to synthesize vitamin D. In the present study, $PM_{2.5}$ exposure had a considerable impact on VDD among obese pregnant women. Vitamin D metabolites can be retained in excess body fat, and cholecalciferol produced in the skin or obtained through diet was partially isolated by body fat before it is carried to the liver for the first hydroxylation (Wortsman et al., 2000). Based on this hypothesis, changes in vitamin D reserves and serum levels of 25(OH)D may be directly associated with the amount of subcutaneous fat. The results of a study by Wortsman et al. (Wortsman et al., 2000) found a relatively small increase in serum levels of 25(OH)D in individuals with obesity after exposure to sunlight.

Our study has several advantages. This was a retrospective study with relatively large sample size. Additionally, the DLNM modeling framework enabled the authors to flexibly examine the exposure and cumulative effects of different gestational weeks. Despite these strengths, this study also has some potential limitations. First, the air pollution level was modeled using only the maternal residential address. Therefore, there might be bias and misclassifications as we are unable to explain other sources that may lead to personal exposures that occur in commuting, work, and other places. Second, no statistical adjustments were made for eating habits, although vitamin D supplementation was used as a covariate-adjusted model. Finally, since most of our study population was Chinese, we could not investigate racial modification owing to a lack of minority representation.

5. Conclusion

Results of the present study presented suggestive evidence that $PM_{2.5}$

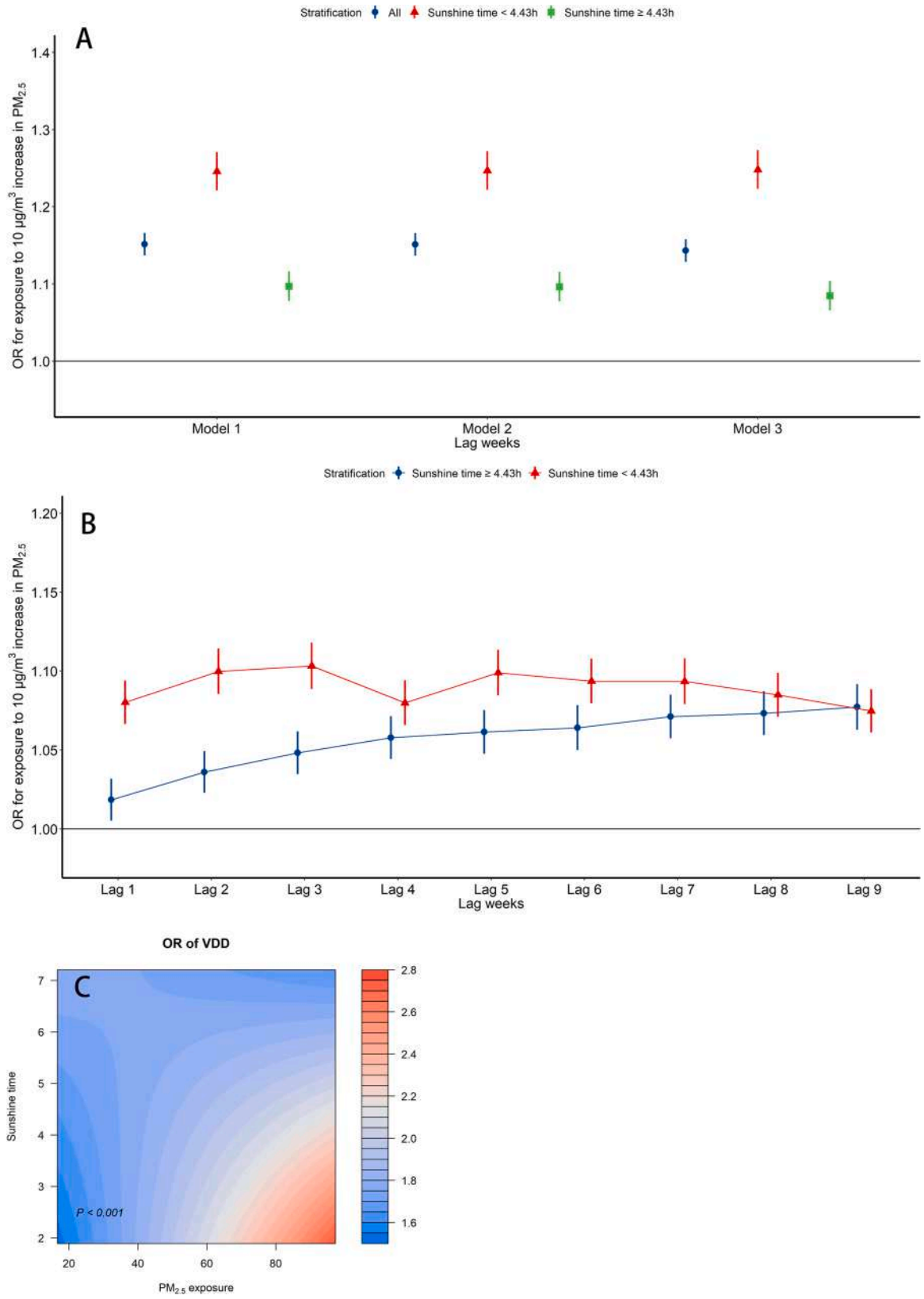

Fig. 4. The interaction between $PM_{2.5}$ exposure and sunshine time. A: The odds ratios of VDD for exposures to average $PM_{2.5}$ in 1–10 weeks before detected for 25(OH)D; B: The odds ratios of VDD for exposures to average weekly-specific $PM_{2.5}$ from 1 to 10 weeks before detected for 25(OH)D; the heatmap of interaction between $PM_{2.5}$ exposure and sunshine time to VDD. Sunshine times are divided into two groups < 4.43 h (N = 30,780) and ≥ 4.43 h (N = 27,245). Model 1 in Fig. A adjusted for pregnant age, parity, gravidity, education level, insurance type, number of fetuses, detected season, smoking, and drinking; Model 2 in Fig. A adjusted for in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Model 3 in Fig. A adjusted for in addition to the confounders in adjusted model 2, Vitamin D supplement (Yes/No) was also adjusted. Models in Figs. B and C adjusted for the confounders were the same as the adjusted model 1 in figure A.

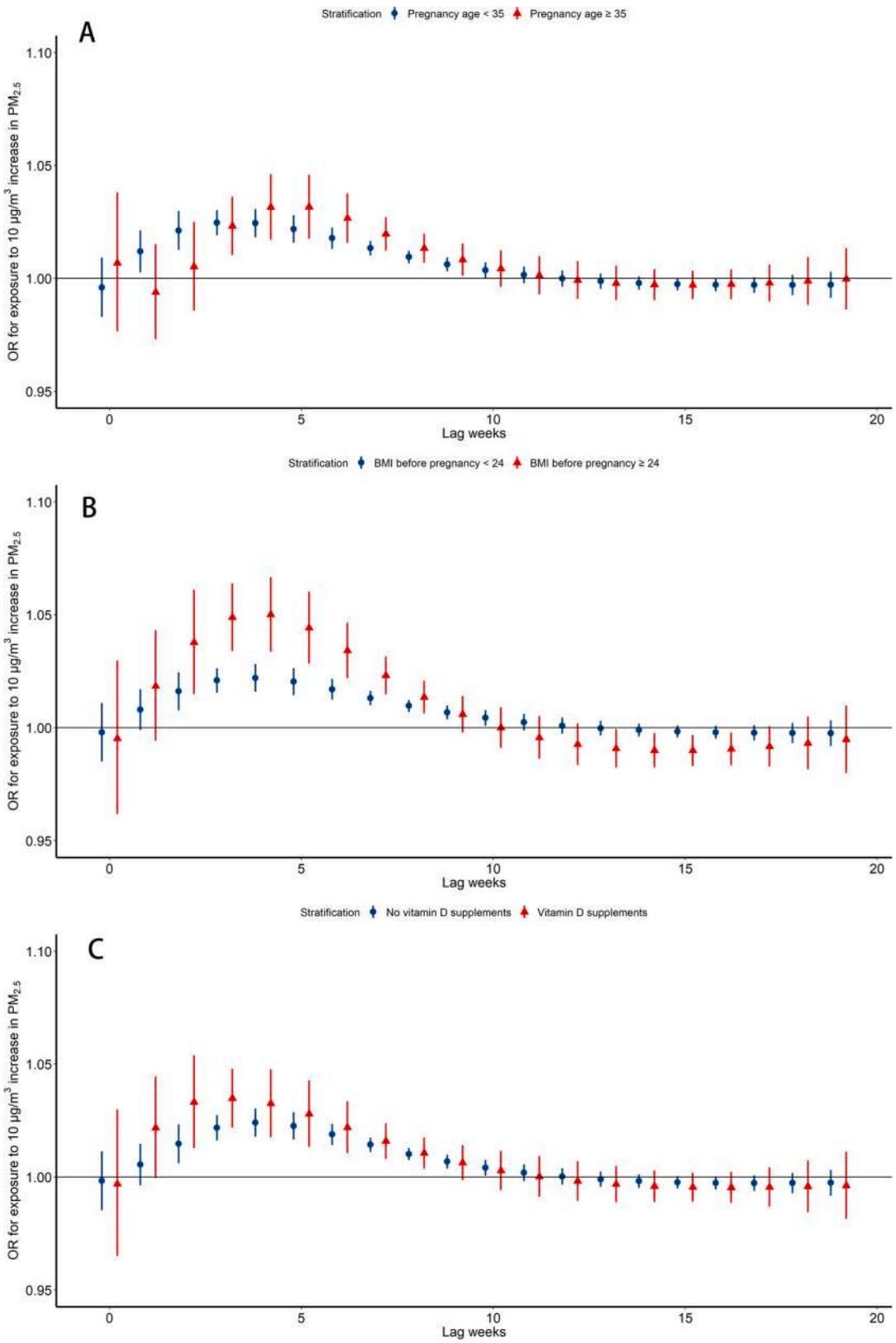

Fig. 5. Odds ratios of VDD in association with weekly-specific prenatal exposure to $PM_{2.5}$ during and before pregnancy, stratified by pregnancy age [A, <35 (N = 48,898) and ≥ 35 (N = 9123)], pre-pregnancy BMI [B, <24 (N = 49,794) and ≥ 35 (N = 7889)], and vitamin D supplementation [C, Yes (N = 9203) and No (N = 48,822)]. Model 1 adjusted for pregnant age, parity, gravidity, education level, insurance type, number of fetuses, detected season, smoking, and drinking; Model 2 adjusted for in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Model 3 adjusted for in addition to the confounders in adjusted model 2, Vitamin D supplement (Yes/No) was also adjusted; Stratification factors were not in the adjustment covariates.

exposure before 1–10 weeks of 25(OH)D detection may reduce the total circulating 25(OH)D level and increase the risk of VDD in pregnant women. The association was more pronounced in weather conditions with less sunshine. Future research to validate these findings and identify the public health impact is warranted.

CRediT authorship contribution statement

Dongjian Yang, Ya Yang: Formal analysis, Software, Writing – original draft. **XinHua Ji, Meng Xia, Lei Chen, Mengxiang Li, Jingjin Shi, Dongjian Yang**: Data curation. **XinHua Ji, Lei Chen**: Term, Conceptualization, Funding acquisition. **Dongjian Yang, Yuechang Yang, Lei Chen, Xinhua Ji**: Writing – review & editing. All authors reviewed the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.113642.

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