Original Article

Vitamin D nutritional status in early pregnancy and its relationship with periconceptional multiple micronutrients supplementation

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Background and Objectives: To assess the vitamin D nutritional status (VDN) of pregnant women in early pregnancy and investigate the effects of periconceptional supplementation with multiple micronutrients (MMs) on this status. **Methods and Study Design:** Data were taken from the Pregnancy Health Care System and Hospital Information System in 2018 in Beijing. Vitamin D nutritional status in early pregnancy was evaluated among 4,978 pregnant women, and 4,540 women who took folic acid only (FA) or multiple micronutrients supplements (MM) during the periconceptional period, were included to estimate the associations between periconceptional supplementation with MM and prevalence of vitamin D deficiency or insufficiency with logistic regression model. **Results:** The mean early-pregnancy vitamin D concentration was 18.6 (±7.5) ng/mL, and the rates of deficiency and insufficiency were 31.6% and 60.5%, respectively. Compared to the FA group, the adjusted odds ratio (aOR, 95%confidence interval, CI) for insufficiency or deficiency of the MM group were 0.25(0.18–0.34), and the aOR (95%CI) for deficiency of the MM group were 0.17 (0.12–0.23). Women who took MMs for a longer period of time, at higher frequencies, and with higher compliance scores had lower rates of deficiency and insufficiency. In winter, spring, and autumn, taking MMs could reduce deficiency by about 70%; in summer, there was little effect. **Conclusions:** Among women in Beijing, serum concentrations of vitamin D in early pregnancy are relatively low, and the rates of deficiency and insufficiency are high. Taking MMs during the periconceptional period could improve this situation.

Key Words: multiple micronutrients supplement, vitamin D, folate, periconceptional period, real-world study

INTRODUCTION

Vitamin D is a type of fat-soluble vitamin that is available in two major forms, namely ergocalciferol-D-2 (vitamin D-2) and cholecalciferol-D-3 (vitamin D-3).[1] D-2 is mainly obtained from plants and vegetables while D-3 is primarily self-synthesized under sunlight exposure (ultraviolet radiation b (UVB) radiation). Both forms of vitamin D can also be obtained through dietary supplements. Vitamin D has various physiological functions. Besides its traditional function of maintaining calcium and phosphorus balance in the body and enabling bone health, it also offers renal protection, cardiovascular protection, immune regulation, and cancer prevention functions.[2] During pregnancy, it binds to the vitamin D receptor at the placental mother–fetus interface, thereby regulating cell proliferation and differentiation while also regulating the secretion of estrogen, progesterone, prolactin, and chorionic gonadotropin. It also helps to regulate glucose and insulin homeostasis and glucose transport throughout the placenta. Ultimately, vitamin D affects placental growth and fetal development.[3]

Vitamin D deficiency is an issue in every country worldwide. There is a high prevalence of low vitamin D status in infants, children, adolescents, adults and elders worldwide, even in countries with sun exposure all year round.[4,5] In the Middle-East and Asia, vitamin D deficiency in adults is highly prevalent.[6] An even higher prevalence of vitamin D deficiency was found in pregnant women.[7] Although a survey on the nutrition and health status of Chinese residents found that there was improvement in the vitamin D nutritional status (VDN) of pregnant women in China between 2015 and 2017, compared to that of 2010–2012, only 12.6% of pregnant women had sufficient VDN.[8] Physiologically, serum con-

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centrations of vitamin D increase with gestational week.[9] Currently, there are no assessment standards that pertain specifically to the VDN of pregnant women, much less those that take into consideration gestational periods.[10] In addition, information available on VDN surveys is still limited in early pregnancy in northern China. Some studies have found that vitamin D deficiency or insufficiency could be related to increase risk for various obstetric and perinatal complications such as preeclampsia, gestational diabetes, preterm birth, and low birth weight.[11–13] As such, it is very important to determine VDN in early pregnancy to be able to implement precise nutritional intervention programs and improve maternal and fetal health.

Studies have shown that women who take vitamin D supplements during the gestational period have increased serum levels of vitamin D at full term.[14, 15] In recent years, with the socioeconomic development of China and, especially, the implementation of a public health project that aims to supplement mothers with folic acid (FA) to prevent neural tube defects, an increasing number of women are taking FA or multiple micronutrients (MMs) while trying to conceive and during pregnancy.[16] In Beijing, more than 90% of women take nutritional supplements during the periconception period and 50% of such women take MMs,[17] which contains at least two nutrients including vitamin D. However, previous studies have largely addressed the relationship between nutritional supplement intake in mid and late pregnancy and VDN.[14, 18] Few large-scale population-level studies have explored the associations between maternal periconceptional MMs supplementation and VDN in early pregnancy.

In this study, we investigated exactly this topic using data from nearly 5,000 pregnant women in Beijing, China. Our results provide novel data on the early pregnancy VDN of pregnant women in similar regions, and could serve as a reference for women in periconception period who wish to identify appropriate nutritional supplements and adopt appropriate supplementation methods.

METHODS

Data source

Data were taken from the Pregnancy Health Care System and Hospital Information System of the Maternal and Child Health Care Hospital in Tongzhou District, Beijing, China. The Pregnancy Health Care System of the Beijing Municipality is connected to the networked computer information system of community hospitals and maternity hospitals. Upon confirmation of pregnancy, women must register with the system at community hospitals within 13 weeks of gestation. Once registered, a community women's health doctor who has undergone standardized training performs a face-to-face interview with the registrant to collect information on demographics (including ethnicity, age, education level, household registration status, occupation, pre-pregnancy body mass index [BMI] and parity) and nutritional supplement intake (yes/no regarding FA, supplement type [pure FA, MMs], regularity of intake [where regular intake is defined as taking supplements 8 of 10 days], and start date of intake [pre-pregnancy or post-pregnancy]). Whenever pregnant mother visits the maternity hospital for a check-up or delivery procedure, medical personnel record the check-up results and delivery information in the Pregnancy Health Care System. Serum concentrations of vitamin D come from the hospital's laboratory information system.

The study was approved by the institutional review board of Peking University (Approval number: IRB00001052-18010).

Study sample

Women who had attended regular pregnancy check-ups and childbirth procedures at the Maternal and Child Health Care Hospital in Tongzhou District, Beijing, China, between January 1 and December 31, 2018 were eligible for the study. Inclusion criteria included availability of data on serum vitamin D concentration from early pregnancy and accurate personal data. Exclusion criteria were missing data on general demographics or obstetric and gynecological information.

During the reporting period, there were 8,577 mothers enrolled in the Beijing Pregnancy Health Care System who also underwent pregnancy health care and childbirth procedures at the hospital. After screening samples based on inclusion/exclusion criteria, information from 4,978 women was included for analysis. Refer to Figure 1 for the selection process.

Vitamin D concentrations and VDN assessment

Samples (4 mL) of fasting peripheral venous blood were collected from pregnant women and centrifuged at 1500 × g for 15 min within 30 min. The upper serum was put in a brown vessel at 4 ºC and transferred with ice box to Beijing Harmony Health Medical Diagnostics Co., Ltd. for measuring vitamin D (based on 25[OH]D concentrations) using a liquid chromatograph mass spectrometer (LC-MS/MS 6430, Agilent) within 24 h of sample collection. The $r2\geq 0.99$ for standard curve equation. During the testing process, quality-control samples were also tested simultaneously. At least two quality controls for each batch of test samples. If there were more than 60 samples in a single batch, the number of quality control samples were ≥5% of the number of samples. The abovementioned company's test for vitamin D meets all of the quality assessment criteria of the College of American Pathologists.

Less than 20 ng/mL is considered to be deficient, 20–30 ng/mL is considered insufficient, 30–100 ng/mL is considered sufficient, and 100 ng/mL is considered toxic.[10]

Definitions of periconception period and gestational weeks

Periconception period refers to the 14 weeks prior to conception until 10 weeks after conception.[19] Gestational weeks were defined as weeks between the date of testing and the date of the last menstrual period. Clinically, for convenience, gestational weeks are counted from the date of the last menstrual period. As such, the periconception period is commonly 12 weeks prior to the last menstrual period until 12 weeks post-conception, and ≤13 gestational weeks is considered early pregnancy.[20]

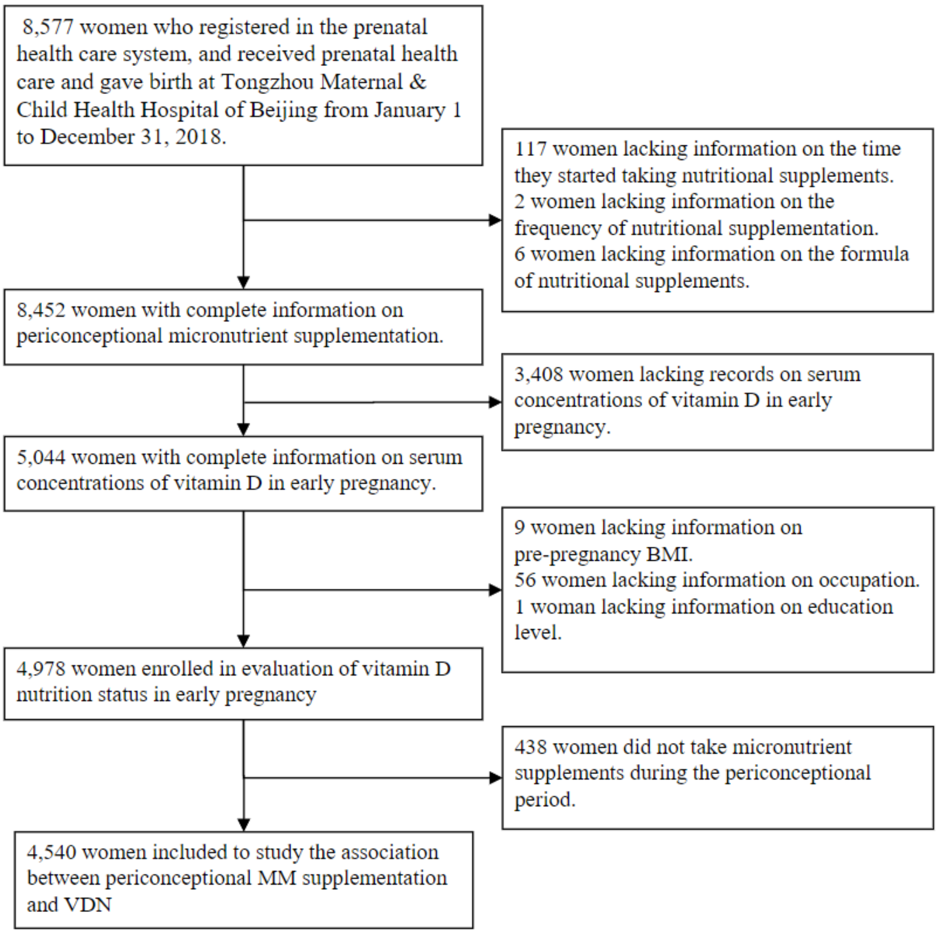

Figure 1. Flowchart of participant selection. MM: multiple micronutrients; VDN: vitamin D nutritional status

Statistical analysis

Statistical analyses were carried out using R4.2.1 (R Foundation for Statistical Computing; http://www.rproject.org). First, the basic characteristics of the study sample were described, after which the Pearson χ2 test was used to compare these characteristics among women who did not take nutritional supplements, women who took FA, and women who took MMs during the periconception period to exclude confounding factors to some extent. Considering the strong relationship between season and VDN, we calculated the mean and median vitamin D concentration according to the season in which the test was performed. These values were then used to describe the early-stage average vitamin D concentration (and its variation) and calculate rates of deficiency and deficiency. To investigate the relationship between supplementation with vitamin D-containing MMs during the periconception period and vitamin D insufficiency or deficiency in early pregnancy, we considered women who took either FA or MMs as our study sample and employed univariate and multivariate logistic regression models to calculate the rough odds ratio (cOR), adjusted OR (aOR), and 95% confidence interval (CI). The multivariate model was adjusted for confounding factors including the basic characteristics of the study sample and the season in which vitamin D was tested, as shown in Table 1. To explore the relationship between adherence to nutritional supplementation during the periconception period and vitamin D concentration, we referred to a previous study[21] and classified the samples into four groups based on adherence scores: those who consistently took FA (0 points), those whose MM supplementation became irregular after pregnancy (1 point), those whose MM supplementation became irregular before pregnancy (2 points), and those who started taking MM regularly before pregnancy (3 points). Because there were a relatively small number of women who began using MM irregularly before pregnancy, this group was combined with women who began using MM irregularly after pregnancy. Then, using the presence or absence of vitamin D deficiency in early pregnancy (Yes=1, No=0) as a dependent variable, a logistic regression model was used to analyze the relationship between MM intake adherence score and vitamin D deficiency. Finally, to further clarify the effect of testing season, we also analyzed the relationship between FA and MM intake and vitamin D concentration and deficiency rates in early pregnancy across different testing seasons. The significance for statistical tests was a two-tailed *p* value of 0.05.

RESULTS

Basic characteristics of the study sample (Table 1)

The average age of the study sample was 29.5±3.9 years old, of which women aged 25–29 years old accounted for the largest percentage (49.4%). The average pre-pregnancy BMI was 22.3±3.4 kg/m^2; 63.2% were within

Table 1. Characteristics of the participants

Characteristics	Total, n (%)†	Supplementation				
		None n (%)	FA n (%)	MM n (%)	$p^{\dagger}$	$p^{\ddagger}$
Ethnic groups					0.04	0.32
Han	4668 (93.8)	422 (96.3)	1472 (94.1)	2774 (93.2)		
Others	310 (6.2)	16 (3.7)	93 (5.9)	201 (6.8)		
Maternal age (year)					0.49	0.59
17–	712 (14.3)	73 (16.7)	205 (13.1)	434 (14.6)		
25–	2457 (49.4)	205 (46.8)	784 (50.1)	1468 (49.4)		
30–	1449 (29.1)	133 (30.4)	458 (29.3)	858 (28.8)		
35–51	360 (7.2)	27 (6.1)	118 (7.5)	215 (7.2)		
Education level					<0.001	0.39
Middle school or lower	413 (8.3)	66 (15.1)	134 (8.5)	213 (7.2)		
High school or technical school	841 (16.9)	113 (25.8)	245 (15.7)	483 (16.2)		
College	1657 (33.3)	131 (29.9)	519 (33.2)	1007 (33.8)		
University or above	2067 (41.5)	128 (29.2)	667 (42.6)	1272 (42.8)		
Household registration					<0.001	<0.001
Both partners are local	2168 (43.6)	144 (32.9)	772 (49.3)	1252 (42.1)		
Only the women are local	1967 (39.5)	206 (47.0)	532 (34.0)	1229 (41.3)		
Only the husbands are local	843 (16.9)	88 (20.1)	261 (16.7)	494 (16.6)		
Occupation					<0.001	0.06
Government agency	422 (8.5)	58 (13.3)	103 (6.6)	261 (8.8)		
Professional technician	972 (19.5)	65 (14.8)	321 (20.5)	586 (19.7)		
Office clerk or related personnel	900 (18.1)	50 (11.4)	307 (19.6)	543 (18.2)		
Business / services	1058 (21.3)	88 (20.1)	331 (21.2)	639 (21.5)		
Unemployment	614 (12.3)	68 (15.5)	174 (11.1)	372 (12.5)		
Others	1012 (20.3)	109 (24.9)	329 (21.0)	574 (19.3)		
Pre-pregnancy BMI					0.02	0.26
Underweight (<18.5 kg/m^2)	493 (9.9)	46 (10.5)	163 (10.4)	284 (9.5)		
Normal (18.5–24 kg/m^2)	3146 (63.2)	247 (56.4)	1013 (64.7)	1886 (63.4)		
Overweight (24–28 kg/m^2)	1035 (20.8)	108 (24.7)	309 (19.8)	618 (20.8)		
Obese (≥28 kg/m^2)	304 (6.1)	37 (8.4)	80 (5.1)	187 (6.3)		
Parity					<0.001	0.22
Nulliparity	2640 (53.0)	171 (39.0)	871 (55.7)	1598 (53.7)		
Multiparity	2338 (47.0)	267 (61.0)	694 (44.3)	1377 (46.3)		
Season of vitamin D test					0.37	0.25
Spring (Mar through May)	1446 (29.1)	124 (28.3)	450 (28.7)	872 (29.3)		
Summer (Jun through Aug)	67 (1.3)	8 (1.8)	26 (1.7)	33 (1.1)		
Autumn (Sept through Nov)	1660 (33.3)	157 (35.8)	535 (34.2)	968 (32.5)		
Winter (Dec through Feb in next year)	1805 (36.3)	149 (34.0)	554 (35.4)	1102 (37.1)		

BMI, body mass index. FA, folic acid. MM, multiple micronutrients.
†Pearson's chi-square test compared among the three groups (none, FA and MM)
‡Pearson's chi-square test compared between the two groups (FA and MM)

the standard range, 9.9% were underweight, and 26.9% were overweight or obese. Overall, 74.8% of women had college degrees or higher. There were statistically significant differences in ethnicity, education, household registration status, occupation, pre-pregnancy BMI, and first vs. multiple pregnancies in the group that did not take supplements, the FA group, and the MM group.

Early pregnancy VDN (Table 2)

The average vitamin D concentration was 18.6±7.5 ng/mL in early pregnancy, with a median of 17.7 ng/mL. Hereafter, we provide means only; see the respective tables for median values. The insufficiency and deficiency rates were 31.6% and 60.5%, respectively. The mean concentration in winter were 16.2±7.4 ng/mL, lower than in all other seasons. Meanwhile, the deficiency rates were significantly higher in winter and spring (67.8% and 63.4%) than in summer and autumn (28.3% and 51.4%).

MM intake during the periconception period and vitamin D concentration in early pregnancy (Table 3)

The mean vitamin D concentrations were 15.4±6.5 ng/mL and 20.5±7.4 ng/mL in the FA and MM groups, respectively, with statistically significant differences between the groups. In the MM group, the early-pregnancy concentrations were higher in those who started taking MMs before pregnancy than in those who took them after pregnancy. Meanwhile, early-pregnancy concentrations of

Table 2. Vitamin D concentrations and nutritional status

Assayed season	n	Vitamin D concentration			Vitamin D nutritional status		
		$\bar{X}$ (SD) (ng/mL)	*Median* (P_{25}– P_{75}) (ng/mL)	*Range (Min–Max)*	Deficiency n (%)	Insufficiency n (%)	Adequate n (%)
Spring	1446	18.0 (7.3)	17.0 (12.1–22.9)	4.4–46.8	917 (63.4)	430 (29.7)	99 (6.9)
Summer	67	25.1 (9.4)	24.4 (18.6–30.9)	6.5–51.1	19 (28.3)	30 (44.8)	18 (26.9)
Autumn	1660	20.3 (7.2)	19.7 (14.9–25.0)	3.5–48.8	853 (51.4)	643 (38.7)	164 (9.9)
Winter	1805	17.3 (7.4)	16.2 (11.6–21.9)	2.8–48.6	1225 (67.9)	468 (25.9)	112 (6.2)
Total	4978	18.6 (7.5)	17.7 (12.7–23.6)	2.8–51.1	3014 (60.5)	1571 (31.6)	393 (7.9)

SD, standard deviation. P25, 25th percentile. P75, 75th percentile.

Table 3. Vitamin D concentrations by status of micronutrient supplementation

Groups	n	$\bar{X}$ (*SD*) (ng/mL)	*Median* (P_{25}– P_{75}) (ng/mL)	Test for trend
Types of supplement		$p<0.001^{‡}$	$p<0.001^{¶}$	
FA	1565	15.4 (6.5)	14.0 (10.6–19.1)	
MM	2975	20.5 (7.4)	19.9 (15.1–25.5)	
Timing of initiation taking MM		$p<0.001^{‡}$	$p<0.001^{¶}$	
After the conception	1770	19.6 (7.1)	18.9 (14.3–24.2)	
Before the conception	1205	21.9 (7.7)	21.4 (16.3–27.2)	
Frequency of tanking MM		$p<0.001^{‡}$	$p<0.001^{¶}$	
High (<8 of 10 days)	1895	19.6 (7.0)	18.9 (14.4–24.1)	
Low (≥8 of 10 days)	1080	22.2 (7.8)	21.6 (16.4–27.6)	
Compliance score†		$p<0.001^{§}$	$p<0.001^{¶}$	$p<0.001$
0	1565	15.4 (6.5)	14.0 (10.6–19.1)	
1	1895	19.6 (7.0)	18.9 (14.4–24.1)	
2	1074	22.2 (7.8)	21.6 (16.4–27.6)	

SD, standard deviation. P25, 25th percentile. P75, 75th percentile. FA, folic acid. MM, multiple micronutrients.
†The compliance score for MM supplementation was divided into: no-use of MM (score=0), used with high frequency and initiated after conception, or used with low frequency and initiated before conception (score=1) and used with high frequency and initiated before conception (score=2), used with low frequency and initiated before conception are combined with the former group for lack of samples.
‡Mann-Whitney U test
§one-way analysis of variance
¶Brown-Mood median test

those who regularly took MMs were higher than those who took FA. Those with higher MM intake adherence scores had higher vitamin D concentrations in early pregnancy. There was an increase in the average concentration from 15.5 ng/mL to 22.2 ng/mL for women with adherence scores of 0 to 2 points.

MM intake in the periconception period and VDN in early pregnancy (Table 4)

The early-pregnancy insufficiency or deficiency rate was 97.0% in women who took FA, and 89.3% in those who took MMs. Compared to the FA group, the aOR (95%CI) for insufficiency or deficiency of the MM group were 0.25 (0.18–0.34), and the aOR (95%CI) for deficiency of the MM group were 0.17 (0.12–0.23). In the MM group, the rates were lower in those who took MMs before pregnancy than in counterparts who started taking them after pregnancy. Finally, women who took MMs at a high frequency and also those who had higher adherence concentrations had lower insufficiency and deficiency rates. Regarding adherence, every one additional adherence point translated into 37% and 70% lower insufficiency and deficiency rates, respectively.

Relationship between MM supplementation during the periconception period and early-pregnancy VDN in different seasons (Table 5)

Among women who were tested for early pregnancy vitamin D concentrations in spring, autumn, and winter, the concentrations were significantly higher in the MM group than in the FA group; the MM group also had a lower deficiency rate. In summer, the vitamin D concentrations of all subjects were significantly higher in the MM group than in the FA group (although the differences in median values were not statistically significant). Differences in deficiency rates were also not statistically significant.

DISCUSSION

The early-pregnancy serum concentrations of vitamin D in Tongzhou District, Beijing, are on the low side, with insufficiency and deficiency rates at 60.5% and 31.6%, respectively. These concentrations are better than those of Nanjing (76.3% deficiency, 23.1% insufficiency), similar to those of Shanghai (53.1% deficiency, 38.5% insufficiency),[22] and poorer than those of Shenzhen (37.8% deficiency), Switzerland (38.9% deficiency, 34.3% insufficiency),[23] and Spain (50.2% deficiency, 30.3% insufficiency).[24]

Compared to the FA group, those who took MMs during the periconception period had higher early-pregnancy vitamin D concentrations and lower rates of insufficiency

Table 4. Association between periconceptional MM supplementation and risk for vitamin D insufficiency or deficiency in early pregnancy

Groups	Total	Adequate	Risk of vitamin D insufficiency or deficiency			Risk of vitamin D deficiency		
	n	n (%)	n (%)	c*OR* (95%*CI*)	a*OR* (95%*CI*)‡	n (%)	c*OR* (95%*CI*)	a*OR* (95%*CI*)‡
Types of supplement								
FA	1565	46 (3.0)	1519 (97.0)	1	1	1215 (77.6)	1	1
MM	2975	319 (10.7)	2656 (89.3)	0.25 (0.18–0.34)**	0.25 (0.18–0.34)**	1493 (50.2)	0.17 (0.13–0.24)**	0.17 (0.12–0.23)**
Timing of initiation taking MM								
After the conception	1770	144 (8.1)	1526 (91.9)	1	1	980 (55.4)	1	1
Before the conception	1205	175 (14.5)	1030 (85.5)	0.52 (0.41–0.66)**	0.49 (0.38–0.63)**	513 (42.6)	0.43 (0.34–0.55)**	0.42 (0.32–0.54)**
Frequency of tanking MM								
Low (<8 of 10 days)	1895	152 (8.0)	1743 (92.0)	1	1	1047 (55.3)	1	1
High (≥8 of 10 days)	1080	167 (15.5)	913 (84.5)	0.48 (0.38–0.60)**	0.45 (0.35–0.58)**	446 (41.3)	0.39 (0.30–0.50)**	0.38 (0.29–0.49)**
Compliance score†				0.42 (0.36–0.49)** §	0.41 (0.35–0.47)** §		0.32 (0.27–0.37)** §	0.30 (0.26–0.35)** §
0	1565	46 (3.0)	1519 (97.0)	1	1	1215 (77.6)	1	1
1	1764	152 (8.0)	1612 (92.0)	0.35 (0.25–0.48)**	0.35 (0.24–1.48)*	1047 (55.3)	0.26 (0.19–0.37)**	0.25 (0.18–0.35)**
2	1074	167 (15.5)	1007 (84.5)	0.16 (0.12–0.23)**	0.16 (0.11–0.22)**	442 (41.2)	0.10 (0.07–0.14)**	0.09 (0.06–0.13)**

cOR, crude odd ratio. aOR, adjusted odd ratio. CI, confidence interval. FA, folic acid.MM, multiple micronutrients

†The compliance score for MM supplementation was divided into no-use of MM (score=0), used with high frequency and initiated after conception, or used with low frequency and initiated before conception (score=1) and used with high frequency and initiated before conception (score=2), used with low frequency and initiated before conception are combined with the former group for lack of samples

‡The confounders adjusted in the multivariate logistic regression model were maternal age, education level, household registration, occupation, pre-pregnancy BMI, parity, season for vitamin D assay. Overweight and Obesity are combined in pre-pregnancy BMI, spring and summer are combined in season for vit. D assay for lack of samples

§compliance score is treated as a continuous value in logistic regression

*p<0.05; **p<0.001.

Table 5. Periconceptional MM supplementation and serum concentrations of vitamin D by seasons

Assayed season	n	$\bar{X}$ (SD) (ng/mL)	*Median* (p_{25}– p_{75}) (ng/mL)	Risk of vitamin D deficiency		
				N (%)	cOR (95%*CI)*	*aOR† (95%CI)*
Spring		p<0.001‡	p<0.001§			
FA	450	14.9 (6.3)	13.6 (10.4–18.2)	359 (79.3)	1	1
MM	872	19.8 (7.3)	19.2 (14.3–24.4)	467 (53.6)	0.29 (0.22–0.38)**	0.28 (0.21–0.37)**
Summer		p=0.003‡	p=0.192§			
FA	26	20.5 (7.3)	21.3 (15.5–27.4)	11 (42.3)	1	1
MM	33	28.6 (9.9)	28.1 (20.7–35.4)	7 (21.2)	0.37 (0.11–1.13)	0.28 (0.04–1.46)
Autumn		p<0.001‡	p<0.001§			
FA	535	17.4 (6.4)	16.5 (12.4–21.4)	374 (69.9)	1	1
MM	968	22.1 (7.0)	21.7 (16.9–26.8)	382 (39.5)	0.28 (0.22–0.35)**	0.28 (0.22–0.35)**
Winter		p<0.001‡	p<0.001§			
FA	554	13.7 (6.0)	12.6 (9.1–16.8)	471 (85.0)	1	1
MM	1102	19.4 (7.4)	18.5 (13.9–24.5)	637 (57.8)	0.24 (0.18–0.31)**	0.24 (0.18–0.31)**

SD, standard deviation. P25, 25th percentile. P75, 75th percentile. cOR, crude odd ratio. aOR, adjusted odd ratio. CI, confidence interval. FA, folic acid. MM, multiple micronutrients

†The confounders adjusted in the multivariate linear regression model in early pregnancy were jethnic groups, maternal age, education level, household registration, occupation, pre-pregnancy BMI, parity. ‡Mann-Whitney U test. §Brown-Mood median test. *p<0.05; **p<0.001

and deficiency. This effect was even more significant among those who had taken MMs for a longer period of time, at higher frequencies, and who had better adherence scores. We were unable to find any published studies on the effect of taking nutritional supplements during the periconception period on early-pregnancy VDN, thus, for the comparative analysis, we used literature on the effects of supplementation during pregnancy on the nutritional status at the mid- or late-pregnancy stages or newborn stage. Our findings are consistent with most such studies,[25–27] although some previous studies have reported that vitamin D supplementation does not increase serum concentrations of vitamin D.[28, 29] One of those, a study conducted in the United Kingdom involving 156 subjects (41 subjects in a vitamin D supplement group and 105 in a control group who did not take vitamin D) explored the effects of taking nutritional supplements containing vitamin D on serum concentration of vitamin D in late pregnancy and relevant indicators such as alkaline phosphatase, calmodulin, parathyroid hormone, and phosphate. They did not find a statistically significant relationship between vitamin D concentration and the concentrations of the relevant indicators. There also were no statistically significant differences between the VDNs of the two groups. These results could have been due to the small sample size of their study. The other study, a large-scale RCT conducted in Bangladesh, reported that taking vitamin D supplements orally in early pregnancy did not improve poor VDN in late pregnancy.[29]

Physiologically, vitamin D-3 is primarily synthesized in the human body under sunlight exposure. As such, seasons (a sunlight-related factor) are an important factor influencing vitamin D concentration and VDN,[30-32] while using sunscreen is related to lower vitamin D concentration.[33] We found that women who went through their early-pregnancy stage in summer had significantly higher vitamin D concentrations than those who experienced that stage in any other season. Furthermore, while taking MMs in spring, autumn, and winter reduced vitamin D deficiency by 72–76%, there were no statistically significant differences between the MM and FA groups in terms of deficiency in summer. These findings might be due to the fact that only 59 women in this study experienced their early-pregnancy stage in summer, and such a (sub)sample size is too small for robust results. We also do not rule out the possibility that more vitamin D may be synthesized by the body with longer duration of sunlight exposure in summer, which in turn reduces the effect of nutritional supplements, which could confound the function of such supplements.

There are several strengths of this study. The sample size was rather large. Other than the small (sub)sample size for testing in summer, there were 1,400 women in every other season. The data are reliable and the testing employed an internationally recognized gold standard method.[34] Furthermore, the vitamin D test results met international quality assessment standards. Finally, the survey on nutritional supplement intake was performed prior to the vitamin D tests, reducing information bias.

However, there are also limitations to mention. We did not collect data on dietary habits, which makes it impossible to rule out any potential effects of vitamin D obtained from the diet from the effects of vitamin supplements alone. Because the participants for the project was women who delivered during January 1 to Dec 31, 2018, they were in their 1st trimester of gestational period during June in 2017 and May 2018 only one month of 1st trimester of gestational period was in summer and serum vitamin D concentration were measured. Rather small number of people tested in summer might be why overall vitamin D concentrations were on the low side and the insufficiency and deficiency rates were quite high. Due to a general lack of data on the precise formulations of supplements taken by the women included in our study, and the overall duration of supplementation, it was impossible to determine the actual dosages of vitamin D taken. The study did not have information on maternal outdoor activities pre and during pregnant period, we could only roughly estimate the dose-response relationship through adherence scores. Finally, this was a single-center study and thus our VDN results are only applicable to women from the region covered in our study (or areas similar to it).

Conclusion

This study assessed the assoication of taking MMs during the periconception period on vitamin D concentration and VDN in early pregnancy. Although the MM intake rate was rather high among women in the region studied, their early-pregnancy vitamin D concentrations were still on the low side while insufficiency and deficiency rates were rather high, with more than 90% of women showing deficiency or insufficiency during winter and spring. MM supplementation during the periconception period may increase the vitamin D concentrations of women in early pregnancy and reduce insufficiency and deficiency rates to some extent, while starting supplementation before pregnancy and adhering to it produces better results. However, with or without MM supplementation, the VDNs of women were significantly better in summer and autumn than in spring and winter. As such, besides taking nutritional supplements, spending more time outdoors and getting more sun exposure is also an important way to improve VDN.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that there are no conflicts of interest exist in relation to the publication of this paper.

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