Tracking of 25-hydroxyvitamin D status during pregnancy: the importance of vitamin D supplementation[1]

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ABSTRACT

Background: The role of maternal 25-hydroxyvitamin D [25(OH)D] in fetal development is uncertain, and findings of observational studies have been inconsistent. Most studies have assessed 25(OH)D only one time during pregnancy, but to our knowledge, the tracking of an individual's 25(OH)D during pregnancy has not been assessed previously.

Objective: We determined the tracking of serum 25(OH)D from early to late pregnancy and factors that influence this.

Design: The Southampton Women's Survey is a prospective mother-offspring birth-cohort study. Lifestyle, diet, and 25(OH)D status were assessed at 11 and 34 wk of gestation. A Fourier transformation was used to model the seasonal variation in 25(OH)D for early and late pregnancy separately, and the difference between the measured and seasonally modeled 25(OH)D was calculated to generate a season-corrected 25(OH)D. Tracking was assessed with the use of the Pearson correlation coefficient, and multivariate linear regression was used to determine factors associated with the change in season-corrected 25(OH)D.

Results: A total of 1753 women had 25(OH)D measured in both early and late pregnancy. There was a moderate correlation between season-corrected 25(OH)D measurements at 11 and 34 wk of gestation ($r = 0.53$, $P < 0.0001$; $n = 1753$). Vitamin D supplementation was the strongest predictor of tracking; in comparison with women who never used supplements, the discontinuation of supplementation after 11 wk was associated with a reduction in season-corrected 25(OH)D ($\beta = -7.3$ nmol/L; $P < 0.001$), whereas the commencement ($\beta = 12.6$ nmol/L; $P < 0.001$) or continuation ($\beta = 6.6$ nmol/L; $P < 0.001$) of supplementation was associated with increases in season-corrected 25(OH)D. Higher pregnancy weight gain was associated with a reduction in season-corrected 25(OH)D ($\beta = -0.4$ nmol $\cdot$ L^{-1} $\cdot$ kg^{-1}; $P = 0.015$), whereas greater physical activity ($\beta = 0.4$ nmol/L per h/wk; $P = 0.011$) was associated with increases.

Conclusions: There is a moderate tracking of 25(OH)D status through pregnancy; factors such as vitamin D supplementation, weight gain, and physical activity are associated with changes in season-corrected 25(OH)D from early to late gestation. These findings have implications for study designs and analyses and approaches to intervention studies and clinical care. *Am J Clin Nutr* 2015;102:1081–7.

Keywords: pregnancy, supplementation, tracking, vitamin D, epidemiology, osteoporosis

INTRODUCTION

Tracking describes the stability of a measurement relative to the population distribution over time. As such, if a biological marker is known to track highly, one measurement can be used to predict future measurements and, therefore, inform the need for interventions to prevent high or low levels. Many studies have investigated the role of serum 25-hydroxyvitamin D [25(OH)D] concentration in a wide range of clinical outcomes (1, 2); the majority of observational investigations have used only a single measurement of 25(OH)D, and yet the tracking of 25(OH)D is not currently well understood. A high correlation between 25(OH)D concentration in samples obtained in the same month at 1–5-y intervals has been shown in adults (3–5). However, it is well recognized that, at latitudes far from the equator, 25(OH)D displays a seasonal variation at the population level (6, 7). To our knowledge, there are no data in any population group that have shown the tracking of an individual's 25(OH)D concentration within the population distribution after taking account of the seasonal variation. This research might be of particular relevance during pregnancy when the delineation of trimester specific effects has major practical relevance.

[1] Supported by grants from the Medical Research Council, British Heart Foundation, Arthritis Research UK, the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, the University of Southampton and University Hospital Southampton National Health Service Foundation Trust, and the NIHR Musculoskeletal Biomedical Research Unit, University of Oxford. Work that led to these results was supported by the European Union's Seventh Framework Programme (FP7/2007-2013) projects EarlyNutrition and ODIN (Food-Based Solutions for Optimal Vitamin D Nutrition and Health through the Life Cycle) under grant agreement numbers 289346 and 613977, respectively.

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Received May 15, 2015. Accepted for publication August 26, 2015.

First published online September 23, 2015; doi: 10.3945/ajcn.115.115295.

There is a wealth of observational data from studies that assessed the relations between maternal serum 25(OH)D and obstetric complications and offspring development (2, 8). These studies have not consistently shown that higher serum 25(OH)D in pregnancy is associated with improved clinical outcomes for either the mother or offspring. However, the timing of a maternal 25(OH)D measurement varies between data sets from early gestation to delivery and across seasons, and this adds complexity to the comparison of results from different studies. Despite the few data available from intervention studies that have shown clinical benefits of antenatal vitamin D supplementation (2, 8), many national guidelines recommend vitamin D supplementation to all women in pregnancy (9–11). As such, the knowledge regarding the tracking of 25(OH)D during pregnancy might enable a clearer interpretation and comparison of studies with inconsistent findings for the same outcome and may influence the development of future supplementation policies. Therefore, we assessed the tracking of 25(OH)D from early to late pregnancy in the SWS (Southampton Women's Survey), which is a prospective mother-offspring birth-cohort study. In addition, we explored maternal factors that might influence 25(OH)D tracking.

METHODS

The SWS

Details of the study have previously been published (12) but, briefly, the SWS is a population-based, prospective, mother-offspring birth-cohort study that is based in Southampton, United Kingdom (latitude: 50.9°N). Nonpregnant women aged 20–34 y were recruited into the study between April 1998 and October 2002 (n = 12,583) and asked to inform the research center if they became pregnant. The SWS was conducted according to the guidelines of the Declaration of Helsinki, and the Southampton and South West Hampshire Research Ethics Committee approved all procedures (276/97 and 307/97). Written informed consent was obtained from all participating women. The SWS is registered in the Cohort and Longitudinal Studies Enhancement Resources, at birthcohort.net, and in the United Kingdom Medical Research Council cohort directory.

Maternal data

At the prepregnancy interview, details of maternal parity, highest educational attainment, and ethnicity were obtained, and height and weight were measured. For women who became pregnant, assessments were performed at 11 (early pregnancy) and 34 (late pregnancy) wk of gestation. Information on smoking status, alcohol intake, exercise participation, and dietary supplement use was obtained from an interview-administered health and lifestyle questionnaire. Information collected regarding vitamin D supplementation included the brand of supplements used and the frequency of use. The manufacturer's information was used to determine the vitamin D content of the supplements. A validated 100-item food-frequency questionnaire was used to assess dietary intake (13), and from this questionnaire, dietary vitamin D intake was determined by multiplying the frequency of consumption of a portion of each food by its vitamin D content according to the United Kingdom food-composition tables or manufacturers' composition data.

25(OH)D analysis

Nonfasted venous blood samples were obtained at 11 and 34 wk of gestation, and an aliquot of maternal serum was stored at −80°C. All early pregnancy 25(OH)D samples were analyzed in a single batch in 2013, and all late-pregnancy samples were similarly analyzed in a single batch in 2008.

From the early pregnancy samples, serum 25(OH)D was analyzed with the use of HPLC and tandem mass spectrometry; serum samples had an internal standard added, which was followed by protein denaturation by the addition of zinc sulfate and methanol. The internal standard and both $25(OH)D_2$ and $25(OH)D_3$ were extracted into hexane, which was dried and reconstituted in the mobile phase. The extracts were analyzed with the use of liquid chromatography with detection by tandem mass spectrometry (Waters). From the late-pregnancy samples, serum 25(OH)D concentrations were analyzed with the use of a radioimmunoassay (Diasorin). This assay measures both $25(OH)D_2$ and $25(OH)D_3$. Total 25(OH)D was calculated from the sum of $25(OH)D_2$ and $25(OH)D_3$ for both early and late pregnancy. The laboratories that undertook both analyses are members of the Vitamin D External Quality Assurance scheme, and both assays met the requirements of this scheme. Intra-assay and interassay CVs for both methods were <10%.

Statistical analysis

Maternal characteristics for women with and without serum 25(OH)D status in pregnancy were compared with the use of t, Mann-Whitney U, and chi-square tests for normally distributed, nonnormally distributed, and categorical outcomes, respectively. Fourier transformations were used to model the seasonal variation in $\log_e$[25(OH)D] for early and late pregnancy. The difference of the measured 25(OH)D from the seasonally modeled 25(OH)D for the exact date of sampling was calculated for each participant to generate a season-corrected 25(OH)D. The tracking of both $\log_e$[25(OH)D] and season-corrected 25(OH)D from early to late pregnancy were assessed with the use of the Pearson correlation coefficient (14). A Bland-Altman plot was also used to assess the agreement between season-corrected 25(OH)D in early and late pregnancy (15). Maternal factors that were associated with the change in season-corrected 25(OH)D were assessed with the use of simple linear regression, and predictors with $P < 0.20$ were included in a multiple linear regression model. Finally, we assessed differences in maternal characteristics according to vitamin D–supplement use with an ANOVA and chi-square test.

All analyses was performed in Stata software (v13; StataCorp LP). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 3158 women who were participating in the SWS delivered a liveborn singleton infant. Serum 25(OH)D concentration was assessed in 2019 women (64.0%) and 2328 women (73.7%) in early and late pregnancy, respectively. A total of 1753 women had 25(OH)D measured in both early and late pregnancy. Characteristics of these women are shown in **Table 1**. Compared with women who delivered a live birth in the study but who did not have 25(OH)D measured in both

TABLE 1
Characteristics of women included in the analysis and, when available, compared with women from the SWS for whom serum 25(OH)D was not measured in both early and late pregnancy[1]

	25(OH)D measured in both early and late pregnancy	25(OH)D not measured in early and late pregnancy	*P*
n	1753	1405	—
Maternal age at delivery, y	30.4 ± 3.7[2]	31.0 ± 4.0	<0.001
White ethnicity, %	96.8	94.0	<0.001
Education to degree level or higher, %	22.2	21.7	0.74
Nulliparous, %	48.3	54.6	<0.001
Prepregnancy BMI, kg/m^2	24.2 (21.9–27.4)[3]	24.1 (21.8–27.3)	0.28
Current smoker, %			
Early pregnancy	13.9	19.2	<0.001
Late pregnancy	13.5	—	—
Consumed alcohol in past 14 wk, %			
Early pregnancy	80.1	—	—
Late pregnancy	77.9	—	—
Moderate/strenuous exercise, h/wk			
Early pregnancy	1.25 (0.25–3.25)	—	—
Late pregnancy	0.75 (0.13–2.25)	—	—
Weight gain from early to late pregnancy, kg	10.7 ± 4.3	—	—
Dietary vitamin D intake, IU/d			
Early pregnancy	129 (91–169)	—	—
Late pregnancy	135 (98–178)	—	—
Vitamin D–supplementation use, %			
Early pregnancy	37.3	—	—
Late pregnancy	22.2	—	—
Serum 25(OH)D, nmol/L			
Early pregnancy	61 (43–81)	—	—
Late pregnancy	59 (41–84)	—	—

[1]*P* values were determined with the use of *t*, Mann-Whitney *U*, and chi-square tests for normally distributed, non-normally distributed, and categorical outcomes, respectively. SWS, Southampton Women's Survey; 25(OH)D, 25-hydroxy-vitamin D.
[2]Mean ± SD (all such values).
[3]Median; IQR in parentheses (all such values).

early and late pregnancy, the women included in this analysis were younger, of higher parity, and less likely to have smoked in early pregnancy (Table 1).

Seasonal modeling of 25(OH)D in pregnancy

In both early pregnancy and late pregnancy, 25(OH)D displayed significant seasonal variation (**Figure 1**). The Fourier-series model explained 17% ($P < 0.0001$) and 30% ($P < 0.0001$) of the variance in 25(OH)D in early and late pregnancy, respectively. The mean ± SD difference between measured 25(OH)D and that modeled by the Fourier series for the date of sampling in early pregnancy was 4.6 ± 23.3 nmol/L (range: −61.2 to 146.0 nmol/L) and that in late pregnancy was 4.8 ± 25.7 nmol/L (range: −66.2 to 182.7 nmol/L).

Tracking of 25(OH)D status from early to late pregnancy

The correlation coefficient between measured 25(OH)D in early and late pregnancy was low ($r = 0.21$; 95% CI: 0.17, 0.26; **Figure 2**). However, season-corrected 25(OH)D was more highly correlated from early to late pregnancy ($r = 0.53$; 95% CI: 0.50, 0.57; Figure 2). **Figure 3** illustrates the agreement between the season-corrected 25(OH)D in early and late pregnancy with the use of a Bland-Altman plot.

Maternal determinants of change in season-corrected 25(OH)D

A number of maternal factors were associated with the change in season-corrected 25(OH)D (**Table 2**), but only the timing of maternal vitamin D–supplementation use, exercise in late pregnancy, and pregnancy weight gain remained significantly associated in the multivariate analysis (Table 2). Thus, compared with women who never took supplements, the discontinuation of vitamin D supplements after early pregnancy blood sampling was negatively associated with the change in season-corrected 25(OH)D ($\beta = -7.3$ nmol/L; $P < 0.001$), whereas the continuation ($\beta = 12.6$ nmol/L; $P < 0.001$) or start of supplementation ($\beta = 6.6$ nmol/L; $P < 0.001$) was positively associated with the change in season-corrected 25(OH)D. Women who either never started or discontinued taking supplements during pregnancy were younger, less-well educated, more likely to smoke in early pregnancy, and less likely to be in their first pregnancy than were women who continued supplementation throughout pregnancy (**Table 3**).

DISCUSSION

In this large prospective cohort study, we have shown that there was moderate tracking of serum 25(OH)D status from early to late pregnancy, and the change in deviation from the modeled

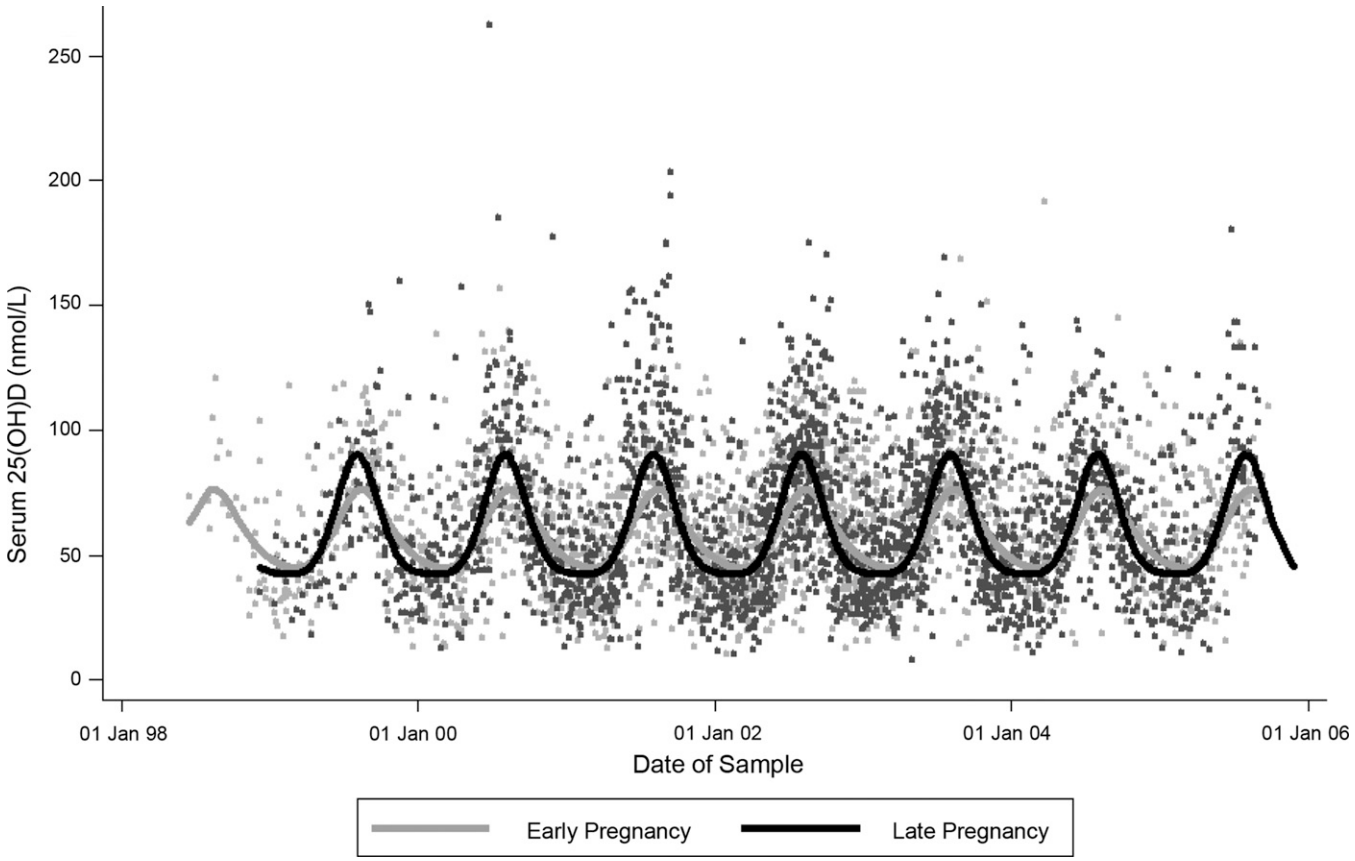

FIGURE 1 Seasonal variation in maternal serum 25(OH)D status in early and late pregnancy (n = 1753). Fourier transformations were used to model the seasonal variation in $\log_e$[25(OH)D] for early and late pregnancy. 25(OH)D, 25-hydroxyvitamin D.

seasonal average of an individual may be influenced by vitamin D supplementation, weight gain, physical activity, and dietary vitamin D intake. To our knowledge, no previous studies have investigated the longitudinal tracking of 25(OH)D status either during pregnancy or between seasons in other population groups.

There have been several small studies, which included between 10 and 40 women, that have attempted to describe the effect of pregnancy on 25(OH)D status (16–18), but the findings have been contradictory. However, the interpretation of these studies has been limited by the recruitment of all women during the same season or insufficient account having been taken of the season of blood sampling. Furthermore, none of these studies considered tracking at the individual level. In nonpregnant adults, 3 studies have shown high levels of 25(OH)D tracking when measured in the same month over several years (3–5), although Hofmann et al. (5) showed that the correlation coefficient was reduced with an increasing number of years between sampling.

Our finding could have an important clinical use; in combination with population data across seasons, a single measurement of 25(OH)D could be used to identify women who are at risk of low concentrations of 25(OH)D at other stages of pregnancy. Thus, appropriate counseling regarding the need for vitamin D supplementation could be provided.

We observed that changes in supplement use strongly influenced 25(OH)D stability relative to the population distribution. Women who either did not use vitamin D supplementation or stopped supplementation after early pregnancy were younger, less-well educated, more likely to smoke, and less likely to be in their first pregnancy and had higher prepregnancy BMI. Previous cross-sectional studies have identified that younger age (19), higher BMI or weight (20–22), smoking (6, 20–22), and lower educational achievement (20) increase risk of vitamin D deficiency in pregnancy, whereas a higher parity is protective (22). Although the majority of women in this study were pregnant before the publication of the United Kingdom Department of Health guidelines that suggest that all women should receive vitamin D supplementation in pregnancy (9), similar demographic factors have also been associated with a reduced likelihood of folic acid supplementation during pregnancy (23, 24). Therefore, there findings highlight a group of women who might require additional health education during early pregnancy.

In addition, we showed that greater weight gain during pregnancy and less exercise in late pregnancy were associated with the downward tracking of 25(OH)D. Adiposity is negatively associated with 25(OH)D in nonpregnant populations, and this association has been hypothesized to result from the sequestration of 25(OH)D within adipose tissue (25). Indeed, vitamin D–supplementation studies have shown that the incremental rise in 25(OH)D was lower in obese individuals than in nonobese individuals (26, 27), whereas, conversely, weight loss was associated positively with the change in 25(OH)D (28–30). Thus, although we cannot be certain that greater weight gain represents

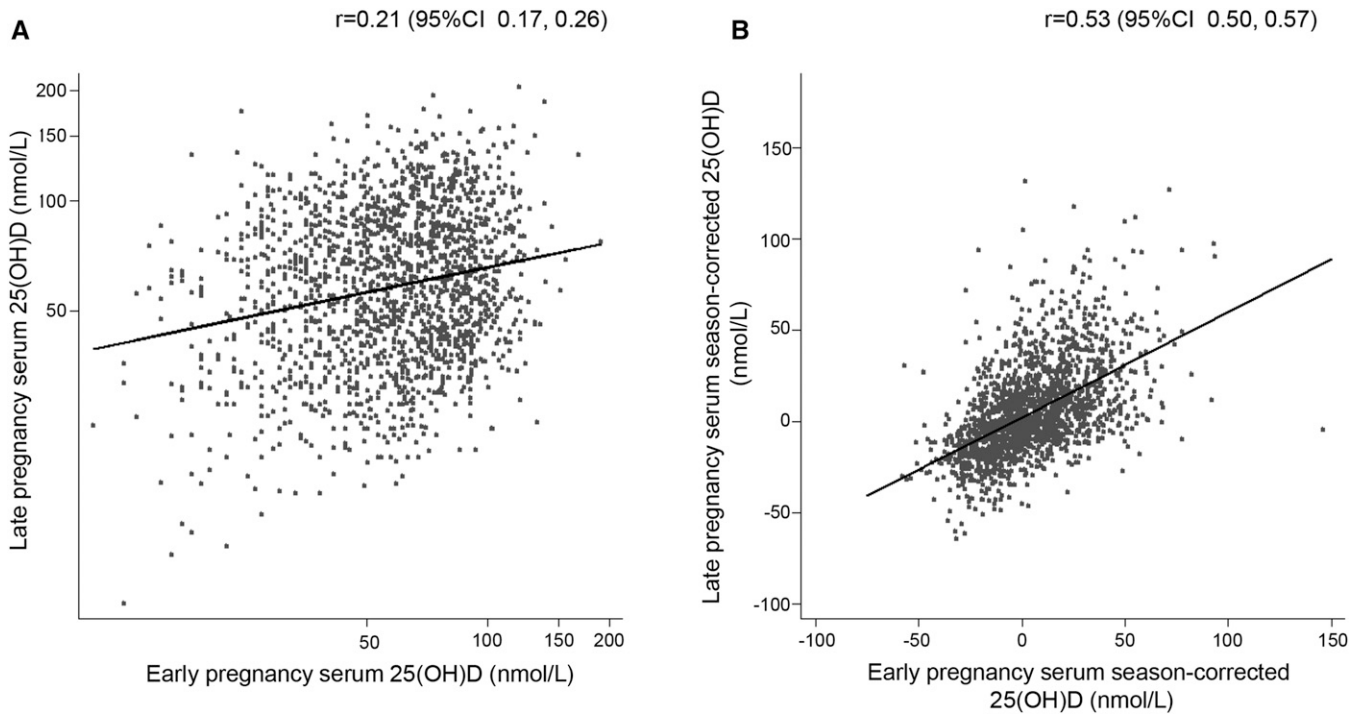

FIGURE 2 Correlation between early and late pregnancy serum 25(OH)D (A) and season-corrected serum 25(OH)D (B) (n = 1753). Correlations were determined with the use of the Pearson correlation coefficient. 25(OH)D, 25-hydroxyvitamin D.

increased fat mass as opposed to fetoplacental tissues, it is likely that the downward tracking of 25(OH)D reflects a higher volume of dilution. Furthermore, this finding suggests that women who gain greater weight in pregnancy might require higher supplementation doses to prevent vitamin D deficiency. This possibility needs to be established in intervention studies.

The strength of this study was in the detailed phenotyping and large number of women included. However, there were a number of limitations that should be considered when interpreting the study. First, the women who participated in the SWS who did not have blood sampling in both early and late pregnancy were older and were more likely to be of nonwhite ethnicity, to be in their first pregnancy, and to smoke in early pregnancy. Therefore, these women were at higher risk of vitamin D deficiency, and our findings are likely to be of particular relevance to this group. It is also likely that the inclusion of such women would have increased the number at the lower end of the 25(OH)D distribution and, thus, yielded greater statistical power. Therefore, although there may be limitations to the generalizability of our finding, there is no reason, to our knowledge, to suppose that the associations observed would have been materially affected. Our findings suggest that women who are at high risk of vitamin D deficiency should be informed that they are likely to remain vitamin D deficient throughout pregnancy unless approaches to increasing their 25(OH)D status are implemented. Second, the women were recruited over a 4-y period. The Fourier transformation used to model the seasonal variation in 25(OH)D assumed that this is the same for each year. However, because of the year-to-year differences in weather, it was unlikely that the pattern was identical every year. Nonetheless, the effect of season was highly significant and accounted for 17–30% of the variation in 25(OH)D. Third, 25(OH)D was measured with different assays in early and late pregnancy with the use of stored, frozen serum samples. However, each model was generated only on the basis of a single assay in a laboratory that was a member of the Vitamin D External Quality Assurance scheme, and therefore, it was unlikely that the use of different assays in early and late pregnancy would have affected the rank change or the tracking coefficient. Furthermore, it has been previously shown that the storage of serum at −80°C does not affect the stability of 25(OH)D (31). Nonetheless, a graphical representation of the

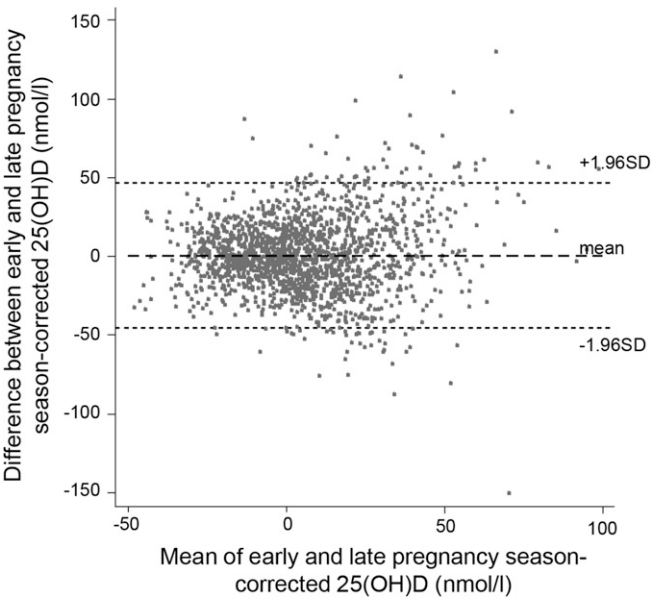

FIGURE 3 Bland-Altman plot that shows the agreement between early and late pregnancy season-corrected serum 25(OH)D (n = 1753). 25(OH)D, 25-hydroxyvitamin D.

TABLE 2
Associations between maternal demographic and lifestyle factors and change in season-corrected serum 25(OH)D during pregnancy[1]

	Δ [season-corrected serum 25(OH)D], nmol/L					
	Univariate[2]			Multivariate[3]		
	n	β (95% CI)	*P*	*n*	β (95% CI)	*P*
Age at delivery, y	1752	−0.0 (−0.3, 0.3)	0.86			
Ethnicity, other vs. white	1753	4.3 (−1.9, 10.5)	0.17	1705	2.4 (−4.0, 8.7)	0.46
Education to degree level or higher, yes vs. no	1750	2.6 (−0.1, 5.3)	0.06	1705	1.8 (−0.8, 4.5)	0.18
Parity, multiparous vs. nulliparous	1752	−0.7 (−2.9, 1.5)	0.54			
Prepregnancy BMI, kg/m^2	1741	0.1 (−0.2, 0.3)	0.52			
Smoking, yes vs. no						
Early pregnancy	1740	−1.7 (−4.9, 1.5)	0.30			
Late pregnancy	1738	−2.1 (−5.3, 1.2)	0.21			
Alcohol consumption, yes vs. no						
Early pregnancy	1736	−2.0 (−4.8, 0.8)	0.15	1705	−2.1 (−4.9, 0.6)	0.13
Late pregnancy	1738	−0.1 (−2.6, 2.7)	0.96			
Moderate/strenuous exercise, h/wk						
Early pregnancy	1732	0.1 (−0.1, 0.4)	0.25			
Late pregnancy[4]	1738	0.4 (0.1, 0.8)	0.01	1705	0.4 (0.1, 0.7)	0.01
Δ Early to late pregnancy	1717	0.9 (−0.1, 0.3)	0.46			
Weight gain from early to late pregnancy,[4] kg	1708	-0.4 (−0.7, −0.1)	0.003	1705	-0.4 (−0.7, −0.1)	0.003
Vitamin D–supplement use compared with never used in pregnancy[4]	1722			1705		
Early pregnancy only		−7.4 (−10.3, −4.5)	<0.001		−7.3 (−10.1, −4.4)	<0.001
Late pregnancy only		11.9 (6.8, 17.0)	<0.001		12.6 (7.5, 17.8)	<0.001
Early and late pregnancy		6.5 (3.5, 9.5)	<0.001		6.6 (3.6, 9.7)	<0.001

[1]25(OH)D, 25-hydroxyvitamin D.
[2]*P* values were determined with the use of univariate linear regression models of season-corrected 25(OH)D on maternal characteristics.
[3]All associations from the univariate analysis with $P \leq 0.2$ were included in the multivariable model.
[4]All associations were significant.

seasonal models of 25(OH)D suggested a higher summer-time peak and a more-flattened winter trough in late pregnancy than in early pregnancy. We cannot be certain whether this was a pregnancy-induced effect or was due to assay differences, and indeed, care should be taken when translating these findings to other populations. Finally, we did not obtain information on the time spent outdoors or on holidays abroad and how this changed during pregnancy.

In conclusion, in this study, we have shown the moderate tracking of 25(OH)D status during pregnancy, which could be used to predict the likelihood of an individual developing low concentrations of 25(OH)D during pregnancy. High-quality

TABLE 3
Maternal characteristics according to vitamin D–supplementation use in pregnancy[1]

	Vitamin D–supplementation use				
	Never	Early pregnancy only	Late pregnancy only	Early and late pregnancy	*P*-between groups[2]
n (%)	1018 (59.1)	327 (19.0)	84 (4.9)	293 (17.0)	—
Early pregnancy season-corrected serum 25(OH)D, nmol/L	−0.1 ± 22.3[3]	9.4 ± 21.2	1.6 ± 20.1	18.5 ± 23.0	<0.0001
Late pregnancy season-corrected serum 25(OH)D, nmol/L	0.0 ± 21.8	2.0 ± 22.2	13.6 ± 27.8	25.0 ± 28.7	<0.0001
Maternal age at delivery, y	30.3 ± 3.8	30.2 ± 3.6	30.3 ± 3.4	31.2 ± 3.5	0.002
White ethnicity, %	96.7	97.3	100	96.6	0.37
Education to degree level or higher, %	17.3	22.6	28.6	36.9	<0.001
Nulliparous, %	40.6	50.5	61.9	70.0	<0.001
Prepregnancy BMI, kg/m^2	24.4 (22.2–27.8)[4]	24.3 (22.0–27.2)	24.0 (22.2–27.8)	23.7 (21.2–25.2)	<0.001
Smoked in early pregnancy, %	18.0	11.3	3.6	4.8	<0.001

[1]Data on supplement use in pregnancy were not available for 31 of 1753 women included in the tracking analysis. These women were similar in age, ethnicity, educational achievement, parity, BMI, and smoking status with those included in the table ($P > 0.05$ for all).
[2]Differences in maternal characteristics according to vitamin D–supplement use were assessed with an ANOVA and chi-square test for continuous and categorical data, respectively. Prepregnancy BMI was not normally distributed; therefore, significance was determined with the use of the log of this variable.
[3]25(OH)D, 25-hydroxyvitamin D.
[3]Mean ± SD (all such values).
[4]Median; IQR in parentheses (all such values).

randomized controlled trials are needed to show whether antenatal vitamin D supplementation can affect clinical outcomes (1, 32). If so, a number of maternal characteristics that have been associated with both 25(OH)D status and the use of supplementation currently exist and should be considered in the provision of public health advice.

We thank G Strange and R Fifield for helping with the preparation of the manuscript.

The authors' responsibilities were as follows—RJM, CC, and NCH: conceived this substudy of the SWS; RJM and SRC: performed the statistical analysis; SMR, HMI, KMG, and CC: conceived, designed, and conducted the SWS; RJM and NCH: wrote the manuscript; CC: had primary responsibility for the final content of the manuscript; and all authors: contributed to the writing of the manuscript and read and approved the final manuscript. KMG has acted as a consultant to Abbott Nutrition and Nestlé Nutrition, has received reimbursements for speaking at an Abbott Nutrition Conference on Pregnancy Nutrition and Later Health Outcomes, at a Nestlé Nutrition Institute Workshop, and at a workshop funded by the International Life Sciences Institute Europe, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. RJM, SRC, EMD, JHD, SMR, HMI, CC, and NCH reported no conflicts of interest related to the study.

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