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Temporal increases in 25-hydroxyvitamin D in midlife women: Longitudinal results from the Study of Women's Health Across the Nation (SWAN)

Deborah M. Mitchell, **Kristin Ruppert**, **Nisha Udupa**, **Fatima Bassir**, **Karin Darakananda**, **Daniel H. Solomon**, **Yinjuan Lian**, **Jane A. Cauley**, **Arun S. Karlamangla**, **Gail A. Greendale**, **Joel S. Finkelstein**, and **Sherri-Ann M. Burnett-Bowie**

Endocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA (D.M.M., N.U., F.B., K.D., J.S.F., S.M.B.), Graduate School of Public Health, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA (K.R., Y.L., J.A.C.), Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, (D.H.S.), Department of Medicine, Division of Geriatrics, University of California, Los Angeles, CA (A.S.K., G.A.G.)

Summary

Objective—25-hydroxyvitamin D (25(OH)D) is critical for bone mineralization and may prevent fractures. Understanding vitamin D deficiency trends in midlife women is particularly important given their concurrent menopausal changes that increase risk for fracture. We aimed to evaluate changes in mean 25(OH)D over time and their determinants in a racially, ethnically, and socioeconomically diverse cohort of midlife women.

Design—A multi-center prospective cohort study.

Patients—1585 women ages 42-52 years at baseline.

Measurements—We measured serum 25(OH)D at 2 timepoints (1998-2000 and 2009-2011). Between-visit change was assessed in the whole cohort and in socioeconomic and demographic subgroups. Among those with vitamin D deficiency (25(OH)D <30 nmol/L) at baseline, we evaluated determinants of persistent deficiency at follow-up.

Results—Mean 25(OH)D increased from 53.8 to 70.0 nmol/L ($p<0.001$), and the prevalence of deficiency decreased from 20.4 to 9.7% ($p<0.001$). While baseline 25(OH)D differed among

Corresponding Author: Deborah M. Mitchell, Endocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA. Telephone: 617-724-2034. dmmitchell@partners.org.

Author Contributions

DMM, JSF, and SMB designed the research, NU, FB, and KD conducted the research, DMM, KR, and YL analyzed the data, DHS, JAC, GAG, and ASK contributed substantially to the design, analytic plan, and data interpretation, DMM wrote the paper, DMM had primary responsibility for final content. All authors read and approved the final manuscript.

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subgroups, the changes in 25(OH)D were similar among groups. The proportion of women reporting dietary supplement use increased from 40.8 to 67.1% ($p<0.001$), and the increase in 25(OH)D was significantly higher in supplement users. Among women with vitamin D deficiency at baseline, White women and supplement users were less likely to remain deficient at follow-up.

Conclusions—Among midlife women, temporal increases in 25(OH)D concentrations are driven largely by increases in supplement use. The proportion of women with 25(OH)D<30 nmol/L and thus at high risk for skeletal consequences remains substantial. Targeted screening for vitamin D deficiency in populations at risk for fragility fracture may be advisable.

Keywords

Humans; Female; Prospective Studies; Vitamin D deficiency; 25-hydroxyvitamin D; Menopause; Dietary Supplements

Introduction

Vitamin D is a critical determinant of calcium absorption and, by extension, bone mineralization[1]. Several researchers have proposed an additional role for vitamin D in extraskeletal health which remains an area of active investigation[2, 3]. Circulating 25-hydroxyvitamin D (25(OH)D), an index of vitamin D sufficiency, is a metabolite of both endogenous vitamin D produced in the skin following ultraviolet light exposure as well as vitamin D from food and supplements[1].

The definition of “adequate” 25(OH)D for bone health is controversial. Imprecision in the standard antibody-based assays of 25(OH)D has also contributed to difficulty in defining requirements[4]. The 2010 Institute of Medicine report suggested that 25(OH)D ≥ 50 nmol/L is sufficient for optimal bone health for the majority of the population[5]; by contrast, recent reports suggest that supplemental vitamin D for fracture prevention benefits only those with 25(OH)D <30 nmol/L[6, 7].

Population-based serial cross-sectional data from the United States NHANES demonstrated a concerning increase in the prevalence of 25(OH)D<30 nmol/L in community-dwelling adults, from 3 to 7% in men and from 7 to 11% in women, over the period spanning 1988-1994 to 2001-2002[8]. Rates of deficiency were higher among Black and Mexican participants in NHANES when compared with White participants[8]; Asian Americans also have an elevated risk of deficiency[9, 10]. Subsequent NHANES surveys found a modest increase in the population mean 25(OH)D in the 2007-8 and 2009-10 samples, coincident with an increase in the use of vitamin-D containing dietary supplements[11].

Women undergoing the menopausal transition have accelerated bone loss, and we have previously shown in the Study of Women’s Health Across the Nation (SWAN) that lower baseline 25(OH)D is associated with increased non-traumatic fracture risk over the next 9.5 years[12]. Improved understanding of population trends in circulating 25(OH)D may inform public health interventions targeting vitamin D status. We here report longitudinal changes in serum 25(OH)D in the SWAN cohort, spanning the period from 1998-2000 to 2009-2011,

using precise and accurate mass spectrometry methodology, and we evaluate the association of socioeconomic and demographic factors with change in 25(OH)D over time.

Materials and Methods

Study participants

SWAN is a multi-site, longitudinal, community-based cohort study initiated in 1996-1997 that enrolled women aged 42-52 years who were pre- or early perimenopausal at baseline[13]. Participants were recruited at 7 sites; each site recruited White women, and women from one additional racial/ethnic group (Black, Chinese, Hispanic, or Japanese). Women who attended Visits 2 (1998-2000) and 12 (2009-2011) and who had serum samples collected for measurement of (25(OH)D) were included in the present analysis (n=1585) (Figure 1). The SWAN study was approved by the Institutional Review Boards at each site and the coordinating center, and all subjects provided written informed consent.

Measurement of 25(OH)D

Blood was drawn in the fasting state prior to 10:00 am. Serum aliquots were stored at −80°C until measurement. 25(OH)D in samples from both Visits 2 and 12 were measured in a single batch by liquid chromatography/tandem mass spectrometry (LC-MS/MS). 25(OH)D was calculated as the sum of $25(OH)D_2$ and $25(OH)D_3$. As previously described, the limit of detection was 3 ng/mL, and the interassay CV was 7.5%[12]. Vitamin D insufficiency was defined as 25(OH)D<50 nmol/L[5], and vitamin D deficiency was defined as 25(OH)D≤30 nmol/L[6].

Ascertainment of multivitamin and vitamin D supplement use

At Visits 2 and 12, use of supplemental vitamins was assessed in standardized interviewer-administered questionnaires and on a worksheet recording medication use. Of note, the format of the worksheet changed between Visits 2 and 12. Vitamin use was coded as “yes” if subjects reported taking either a multivitamin or a vitamin D supplement at least one day per week.

Additional covariates

Age (Visits 2 and 12), race/ethnicity (baseline visit), country of origin (baseline visit), household income (Visits 2 and 12), language use (Visits 2 and 12), educational attainment (baseline visit), and health insurance status (Visits 2 and 12), were assessed by standardized interviewer-administered questionnaires. Height and weight were measured at each visit on calibrated scales and stadiometers, and BMI was calculated. BMI categories were defined as normal weight (BMI <25 kg/m^2), overweight (25 kg/m^2 ≤ BMI <30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). The season of blood draw for each visit was defined as winter (October through March) and summer (April through September).

Statistical Analyses

All data were visually inspected for outliers. Baseline characteristics of the cohort were described with mean and standard deviation for continuous variables and number and

percent for binary and categorical variables. The change in the proportion of subjects taking vitamin D supplements between visits was assessed with McNemar's test.

Differences in 25(OH)D among subgroups at both Visits 2 and 12 were evaluated with ANOVA and were corrected using the Bonferroni method for multiple comparisons. Unadjusted comparisons of Visit 2 and Visit 12 25(OH)D in the whole cohort and in designated subgroups were evaluated with paired t-tests. Differences in Δ25(OH)D among subgroups was evaluated with ANOVA followed by Bonferroni correction. The association of continuous covariates with change in 25(OH)D was assessed with linear regression. Between-visit comparisons of the prevalence of 25(OH)D below the indicated thresholds was assessed with McNemar's test.

A longitudinal mixed model was generated to evaluate the independent association of race/ethnicity group with change in 25(OH)D. The model included age, BMI, educational attainment, household income, language use, insurance status, season of blood draw, study site, and menopausal status.

Women with and without baseline 25(OH)D > 30 nmol/L were compared by t-test for continuous variables (age and BMI), or by χ^2 for binary/categorical variables (country of birth, race/ethnicity group, household income, educational attainment and vitamin use). Logistic regression was used to determine predictors of remaining vitamin D deficient at Visit 12 among subjects who were deficient at Visit 2. Covariates in this model included age, BMI, change in BMI, race/ethnicity group, household income, vitamin use, educational attainment, and Visit 12 season of blood draw. Study site was not included in this model after regression diagnostics determined that it was collinear with race/ethnicity.

Differences in the proportion of women of different race/ethnicity groups taking vitamin supplements at Visit 12 were evaluated with ANOVA.

Results

Clinical and demographic characteristics of the cohort

1585 women were included in the current analysis, of whom 43.1% had vitamin D insufficiency (25(OH)D<50 nmol/L) and 20.4% had vitamin D deficiency (25(OH)D ≤30 nmol/L) at Visit 2 (1998-2000), the first visit at which 25(OH)D was measured (Table 1). The women represented a wide array of racial and ethnic groups, socioeconomic statuses, and levels of formal education. At visit 12 (2009-2011), average age had increased to 60.3 ± 2.7 years, and average BMI had increased to 29.1 ± 7.3 kg/m^2. The distribution of household income was similar to that at Visit 2 (10%, 12%, 13%, 21%, and 44% at < $20,000, 20-35,000, 35-50,000, 50-75,000, and ≥75,000 respectively), and the percentage of subjects who were uninsured was also similar at 5.9%. The proportion of subjects who reported taking multivitamins or vitamin D at the follow-up visit increased from 40.8% to 67.1% (p<0.001). Of note, among all the women who had 25(OH)D measured at visit 2, we did not observe a difference among those who did (n=1585) or did not (n=716) have 25(OH)D measured at visit 12 (53.8 ± 24.3 vs 54.0 ± 24.5 nmol/L, p=0.92).

Change in serum 25(OH)D concentration over time

As shown in Table 2, the mean serum 25(OH)D concentration in the cohort increased by 16.2 nmol/L ($p<0.001$) between Visits 2 and 12. As expected, baseline 25(OH)D varied significantly by race/ethnicity, household income, educational attainment, vitamin use, season of blood draw, and BMI category at each visit. Specifically, Black women had significantly lower mean baseline 25(OH)D compared with Chinese and Hispanic women, who were significantly lower than Japanese and White women. Between visits, we observed a significant increase in 25(OH)D over time in every subgroup investigated with the exception of women who discontinued vitamin use after Visit 2. Within subgroups, we observed significant differences in the absolute change in 25(OH)D concentration (Δ25(OH)D) by race/ethnicity, vitamin use, and season of blood draw. We did not observe differences in Δ25(OH)D when comparing by country of origin, household income, language use, educational attainment, medical insurance status, or BMI category (Supplemental Figure 1). For continuous covariates, we did not observe an association of age or of baseline BMI with Δ25(OH)D (data not shown), but we did observe a small but significant inverse association of change in BMI with Δ25(OH)D, such that women who gained more weight between visits had a smaller increase in 25(OH)D (−0.7 nmol/L per additional kg/m^2, $R=-0.088$, $p<0.001$).

As shown in Figure 2A, in the overall cohort, the percentage of women with vitamin D insufficiency decreased from 43.1 to 23.8% between Visits 2 and 12. In addition, the percentage of women with vitamin D deficiency decreased from 20.4 to 9.7% between visits. As shown in Figures 2B-E, the observed right-shift in the population distribution of 25(OH)D was most evident in the women who either initiated vitamin use after Visit 2 or took vitamins throughout, with limited evident change among the women who never took vitamins or who discontinued vitamin use after Visit 2.

While the cohort mean 25(OH)D increased with time, 25(OH)D decreased in 412 (26.0%) subjects and decreased by more than 25 nmol/L in 71 (4.5%) subjects. Notably, among subjects who were not vitamin D deficient at Visit 2 (n=1261), 64 (5.1%) were newly deficient at Visit 12.

Independent effect of race/ethnicity on Δ25(OH)D

As noted above, we observed substantial variation in baseline 25(OH)D by race/ethnicity group. Therefore, to investigate the effect of race/ethnicity group on Δ25(OH)D, we generated a longitudinal mixed model adjusting for the following: age, BMI, educational attainment, household income, language use, insurance status, and season of blood draw. Study site and menopausal status were included as additional covariates in the mixed model. Compared to Black women, White and Japanese women had a significantly smaller increase in 25(OH)D (8.0 and 6.7 nmol/L smaller increase per 11 years, $p<0.001$ and $p=0.005$, respectively). We did not observe significant differences in the rate of change of 25(OH)D between Black women and either Hispanic or Chinese women (3.0 and 2.7 nmol/L smaller increase per 11 years, $p=0.444$ and $p=0.250$ respectively).

Δ25(OH)D among women with vitamin D deficiency

To further evaluate the women at highest risk for consequences of low serum vitamin D, we assessed Δ25(OH)D among women with vitamin D deficiency at baseline (n=324, 20.4% of cohort, see Table 1). Compared with the women with baseline 25(OH)D>30 nmol/L, the women with deficiency were slightly younger (48.0 vs. 48.7 years, p<0.001), had a higher BMI (31.5 vs. 27.1 kg/m^2, p<0.001), were more likely to have been born in the US (p<0.001), were more likely to be Black and less likely to be White, Chinese, or Japanese, and tended to have lower household income and educational attainment (data not shown). They were also less likely to report using a vitamin supplement (20.7 vs. 45.9%, p<0.001).

Of the 324 women with vitamin D deficiency at baseline, 89 (27.5%) remained deficient when measured again at Visit 12. In univariable analyses, predictors of remaining deficient at Visit 12 included higher baseline BMI (p=0.046), race/ethnicity (p=0.001), household income (p=0.049), and vitamin use (p<0.001). We generated a multivariable logistic regression model for remaining deficient at Visit 12, including all the parameters found to be significant in univariable regressions as well as age, educational attainment, change in BMI, and Visit 12 season of blood draw as other potentially important covariates. Of note, none of the Japanese women with 25(OH)D≤30 nmol/L at baseline (n=14) remained deficient at Visit 12, so these subjects could not be included in the logistic model. As seen in Table 3, race/ethnicity, vitamin use, and increase in BMI over time were independent predictors of remaining deficient at Visit 12. Specifically, compared with Black women, White women were 3.7 fold less likely to remain deficient at Visit 12. Compared with women who never used vitamin supplements, those who either started after Visit 2 or took vitamins throughout were 4.5 and 5.7 fold less likely to remain deficient at Visit 12.

Prevalence of low 25(OH)D at Visit 12 by race/ethnicity and vitamin use status

Given the strong associations of race/ethnicity and vitamin use with serum 25(OH)D, we evaluated the prevalence of low serum 25(OHD) at Visit 12 using a threshold of ≤ 30 nmol/L (deficient) after stratifying by these factors. Of note, the proportion of women who reported taking vitamins differed by race/ethnicity (70%, 56%, 72%, 58%, 77% among White, Black, Chinese, Hispanic, and Japanese women respectively, p<0.001).

As shown in Figure 3, the risk of low 25(OH)D varied substantially by these clinically available variables. Notably, the overall prevalence of deficiency was 23% among women who were not taking vitamin supplements at Visit 12, but the prevalence of deficiency varied dramatically by race/ethnicity, ranging from 5% of Japanese women to 46% of Black women. Among those who did report taking vitamins, the overall prevalence of severe deficiency was 3%, but rose to 9% among Black women taking vitamins.

Discussion

In the SWAN prospective cohort of women in midlife, we observed a significant increase in mean serum 25(OH)D concentrations as measured by LC-MS/MS between the periods 1998-2000 and 2009-2011. The observed increase was clinically meaningful, with approximately 50% reductions in the proportion of women with vitamin D insufficiency and

deficiency. The absolute increase was higher in Black women compared to White and Japanese women, though women of all racial/ethnic groups demonstrated significant increases. The degree of increase did not depend on other social and demographic factors including household income, education, language use, or health insurance status. Use of vitamin D-containing supplements was a major driver of the increase in mean 25(OH)D, with higher increases in subjects who initiated or continued supplement use compared to those who discontinued or never used. Concerningly however, rates of significant deficiency remained high, with almost 10% of the cohort having 25(OH)D≤30 nmol/L at the 2009-2011 visit. Deficiency was particularly high among Black women at ~25% overall, and at 9% even among those using vitamin D-containing supplements.

Our finding of a temporal increase in 25(OH)D is consistent with data from the US population-based NHANES dataset[11]. Of note, in NHANES, the assay methodology was not consistent between samples, and the data are thus mathematically standardized; our data by contrast provide direct evidence of a temporal increase in mean 25(OH)D. Our results are also consistent with the Canadian Multicentre Osteoporosis Study (CaMos), but extend its findings from an almost exclusively White population to additional racial/ethnic groups[14]. Other longitudinal studies, by contrast, show stable or declining 25(OH)D with time[15–17]. The cause of the discrepancies in temporal trends in 25(OH)D between study cohorts is unclear, but may relate to regional differences in dietary patterns, sunlight exposure, and other health-related behaviors.

The period between 1998 and 2011 was marked by significant increases in press reports regarding the health benefits of vitamin D, aimed both at health care providers and at the general public. An emphasis on dietary supplements to achieve adequate body stores of vitamin D was a prominent theme in contemporaneous newspaper articles[18]. Consumer spending on vitamin D supplements in the United States rose from $40 million to $425 million between 2001 and 2009[19]. NHANES data indicate that, while the overall proportion of people taking vitamin D-containing supplements in the US was relatively stable between 1999 and 2012 (37 to 40%), the proportion of people taking vitamin D as an individual supplement rather than as part of a multivitamin increased from 5 to 19%, which may indicate an increase in the absolute amount consumed[20]. Given the strong association of supplement intake with longitudinal change in 25(OH)D in SWAN, the similar increase in 25(OH)D across subgroups of SWAN subjects suggests that outreach regarding the benefits of vitamin D was both accessible and persuasive to women of diverse backgrounds and socioeconomic strata. As our data are from an observational study rather than a supplementation trial, they reflect “real-world” intake of supplements. Our findings of persistent low 25(OH)D among supplement users differ from the results of randomized controlled trials of supplementation[21–23], and may reflect real-world usage. A portion of the increase in 25(OH)D among supplement users may also reflect engagement in other health-promoting behaviors including increased dietary vitamin D intake and/or increased sun exposure. A recent survey of supplement users in NHANES found that supplement users had better self-reported health, more physical activity, and less smoking than non-users, and similar findings have been reported in other populations[24, 25].

Several trials have investigated the dose-response of 25(OH)D to vitamin D supplementation, establishing that White and Black women absorb and metabolize cholecalciferol equivalently, and that the rise in 25(OH)D with supplementation is independent of race and age[21–23]. Supplement-driven increases in 25(OH)D are inversely proportional to baseline 25(OH)D, meaning that, for a given supplement intake, the rise in 25(OH)D is greater among people with a lower baseline[23, 26]. Our observation of a larger increase in 25(OH)D among Black women compared with White and Japanese women, likely thus stems from differences in 25(OH)D at Visit 2.

Our study has several strengths. We used LC-MS/MS to obtain highly accurate and precise measures of 25(OH)D in a diverse cohort of women who were well-phenotyped regarding social and demographic variables. There are limitations as well. We enrolled women at midlife, so these results are not generalizable to men or to women of differing ages. However, women at midlife are quite vulnerable to health consequences of low vitamin D given perimenopausal bone loss with attendant risk of osteoporosis and fracture[27–29]. Our results are also not generalizable to women outside the United States, who may have different sunlight exposure, dietary patterns, and attitudes towards supplement use. For example, despite the Scientific Advisory Committee on Nutrition of the United Kingdom recommending supplementation of 400 IU daily in 2016, only 43% of adults in a recent survey were adhering to this recommendation[30]. We measured total 25(OH)D rather than free or bioavailable 25(OH)D, and we have not measured vitamin D binding protein (DBP). However, it remains unclear whether free or bioavailable 25(OH)D offers additional information beyond total 25(OH)D [21, 31], and most, but not all, studies do not support a significant difference in circulating DBP concentration among individuals of different racial and ethnic backgrounds[32–36]. In addition, the mass spectrometry assay did not specifically exclude 3-epi-25(OH)D, which has been shown to constitute on average 2-3% of total 25(OH)D[37]. We had no information on the dose or duration of use of vitamin D supplements, and the format of the worksheet recording vitamin use changed to include more detailed questions at the later visit, potentially affecting the precision of the measure. We do not have measurements of other factors which may influence serum 25(OH)D including time spent outdoors and sunlight exposure. In particular, differences in climate and/or latitude between sites may influence both these factors. Reassuringly however, we observed no difference in change in 25(OH)D by study site. Additionally, our analysis of the effect of race/ethnicity on change in 25(OH)D was adjusted for study site, suggesting that subgroup-specific differences were independent of climate and latitude. Finally, study participation may have changed SWAN subjects' health-related behaviors[38]. Reassuringly, while BMD was an outcome that was measured at 5 sites, potentially heightening awareness among participants, the subjects enrolled in the 2 sites which did not assess BMD (Chicago and New Jersey) did not differ in their change in mean 25(OH)D over time compared with subjects whose bone density was evaluated (Table 2).

In conclusion, in this cohort at risk for osteoporosis and fragility fractures given their female sex and transition through the menopause, mean 25(OH)D rose significantly and substantially over an 11 year timespan. While we observed expected differences in absolute 25(OH)D, the temporal increase in 25(OH)D was similar in all demographic subgroups, suggesting that public health interventions to raise awareness about vitamin D and its health

effects had equitable impact. However, a sizeable proportion of women continued to have 25(OH)D concentrations low enough to put them at risk for skeletal complications of vitamin D deficiency. While considerable controversy exists regarding the optimal 25(OH)D for skeletal health, data suggest that concentrations under 30 nmol/L are associated with osteomalacia[39, 40] and that supplementation of individuals below this threshold improves bone mineral density[6, 7]. Current guidelines do not recommend screening asymptomatic individuals for low 25(OH)D, given the paucity of data indicating population-wide benefit and concern for over-treatment of low 25(OH)D in the absence of true disease[41, 42]. However, our data demonstrating that 9.6% of mid-life women and, in particular, 25.4% of mid-life Black women have 25OHD≤30 nmol/L suggest that more intensive case-finding may be warranted, in order to efficiently target those likely to benefit from supplementation both clinically and in the context of future research studies. Our data suggest that factors including race/ethnicity, socioeconomic status, years of formal education, and supplement use could be used to guide clinicians or health systems to identify women at higher risk of 25OHD<30 nmol/L. These data, if replicated in other cohorts, may prompt revision of current public health guidance and facilitate targeted supplementation strategies to improve bone health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Centers: *University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004;* and the *University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.*

NIH Program Office: *National Institute on Aging, Bethesda, MD – Chhanda Dutta 2016-present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.*

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

SWAN Repository: *University of Michigan, Ann Arbor – Siobán Harlow 2013 - Present; Dan McConnell 2011 – 2013; MaryFran Sowers 2000 – 2011.*

Coordinating Center: *University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.*

Steering Committee: Susan Johnson, Current Chair, Chris Gallagher, Former Chair

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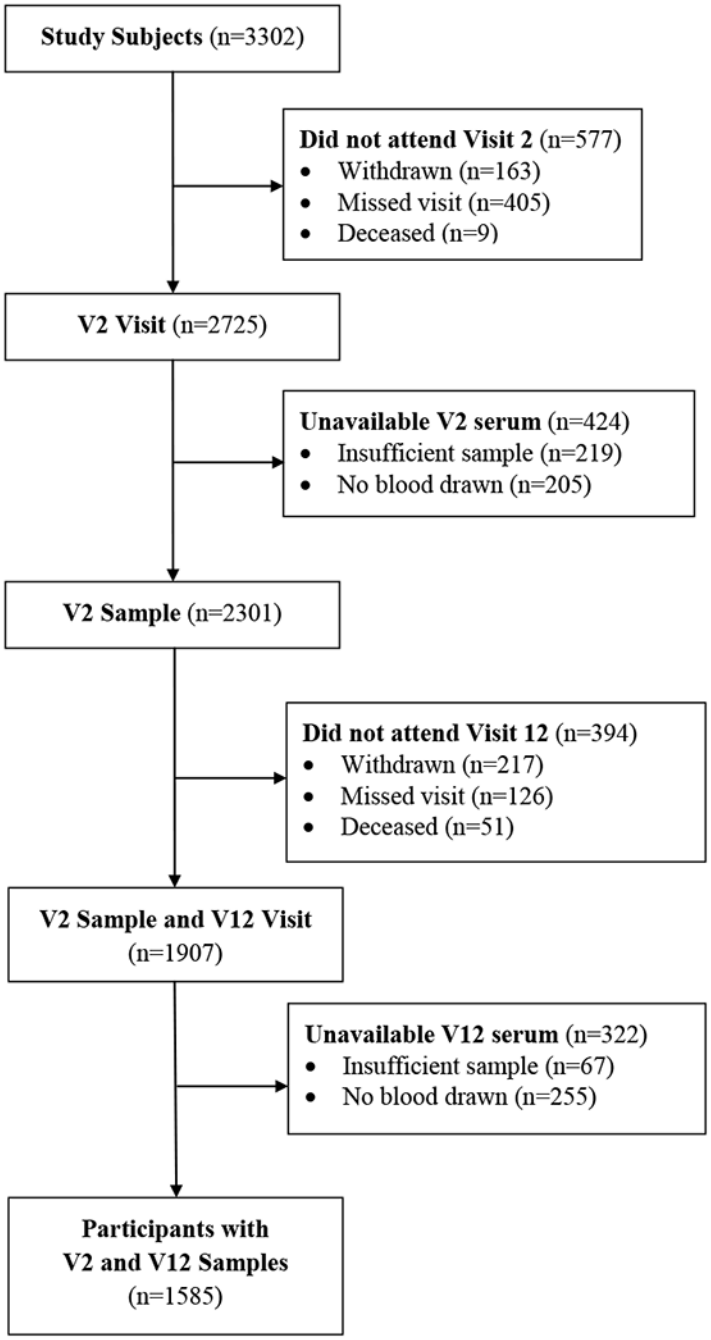

Figure 1.
Flow chart of SWAN participants included in the present analysis.

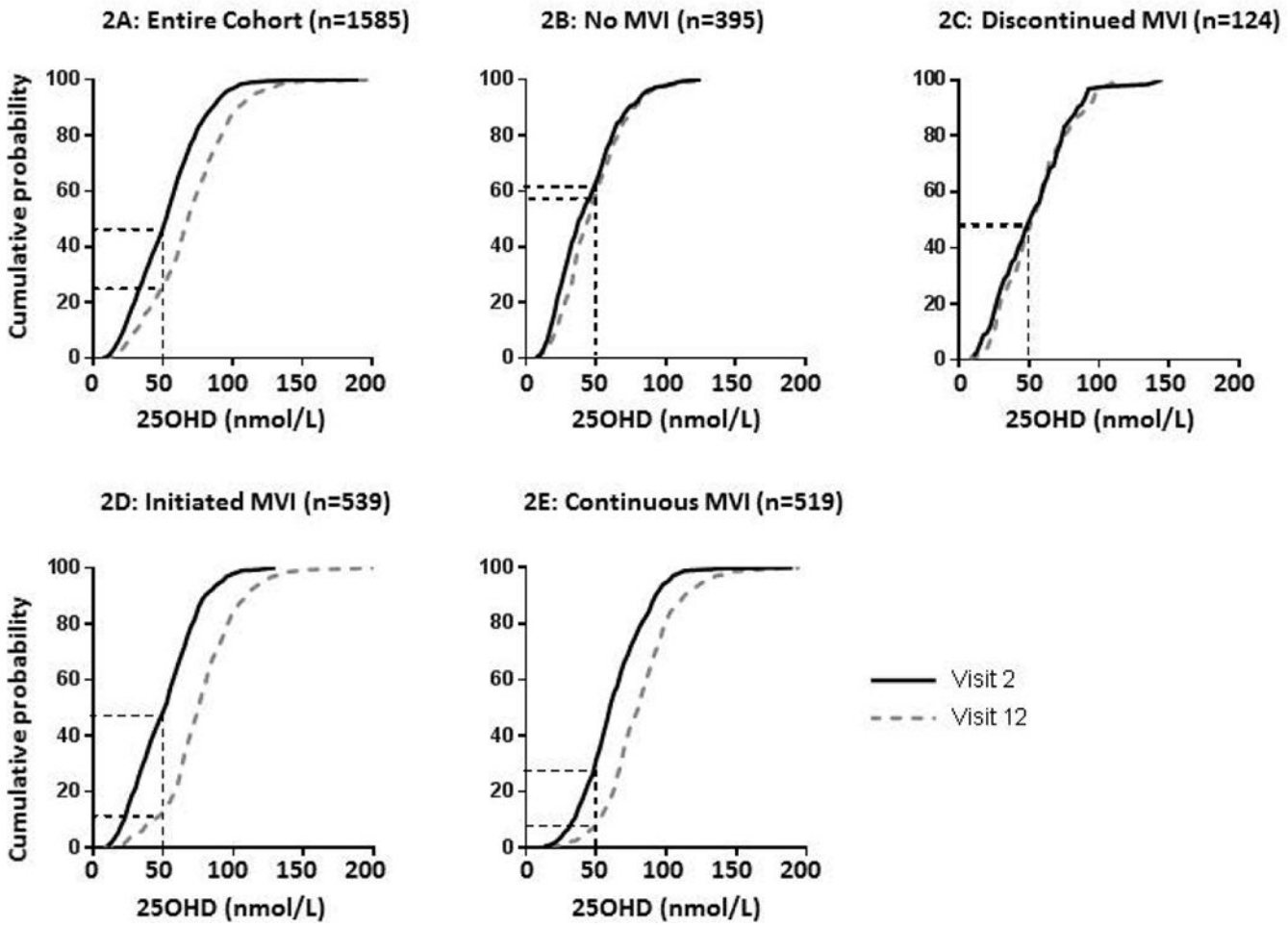

Figure 2.

Cumulative distribution graph of 25-hydroxyvitamin D in the whole cohort (**2A**) and among women who did not use vitamins (**2B**), who discontinued vitamin use after Visit 2 (**2C**), who initiated vitamin use after Visit 12 (**2D**), and who took vitamins at both visits (**2E**). In the cumulative distribution graph, the cumulative frequency along the y-axis represents the proportion of the population with 25(OH)D less than or equal to the corresponding value on the x-axis. Visit 2 in black, Visit 12 in gray. Dotted lines indicate the proportion of subjects with 25-hydroxyvitamin D < 50 nmol/L at each visit. Note that vitamin use information was unavailable for 8 subjects.

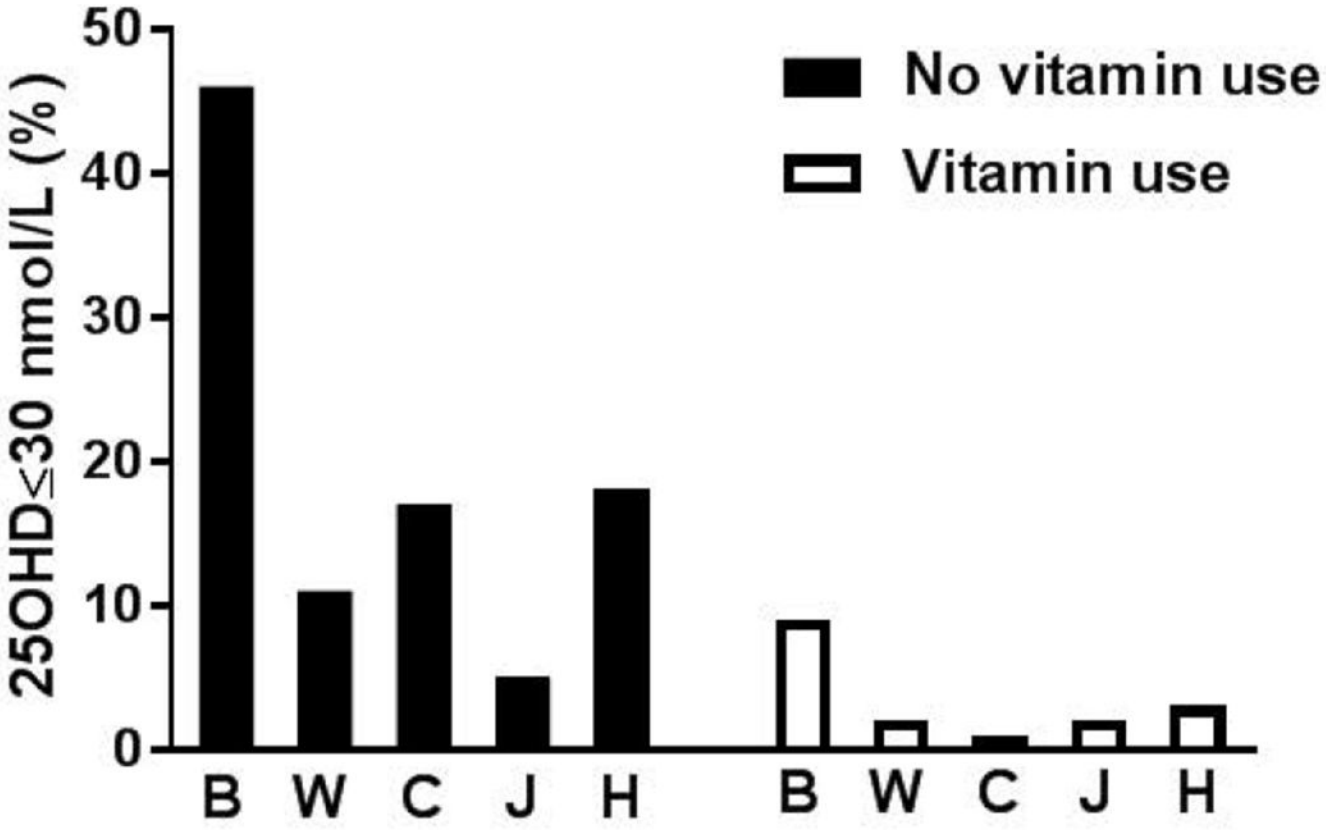

Figure 3.

Bar chart showing the proportion of subjects meeting criteria for low serum 25-hydroxyvitamin D defined as ≤30 nmol/L when stratified by race/ethnicity and vitamin use. B, Black; W, White, C, Chinese; J, Japanese; H, Hispanic

Table 1:

Clinical and Demographic Characteristics

Variable	Mean (SD) or n (%)
Age at V2 (years), mean (SD)	48.6 (2.7)
BMI at V2, kg/m^2, mean (SD)	28.0 (7.2)
Race/ethnicity, n (%)	
Black	386 (24.4)
White	778 (49.1)
Chinese	172 (10.9)
Hispanic	66 (4.2)
Japanese	183 (11.6)
Country of origin, n (%)	
United States	1225 (77.3)
Other	311 (19.6)
Unknown	49 (3.1)
Household income at V2, n (%)	
<$20,000	142 (9.0)
$20,000 to <$35,000	183 (11.5)
$35,000 to <$50,000	236 (14.9)
$50,000 to <$75,000	389 (24.5)
≥$75,000	559 (35.3)
Unknown	76 (4.8)
Language use at V2, n (%)	
Non-English language only	78 (4.9)
English and non-English language	181 (11.4)
English language only	1299 (81.9)
Unknown	27 (1.8)
Educational attainment, n (%)	
Less than high school	69 (4.4)
Completed high school or GED	252 (15.9)
Some college	468 (29.5)
College graduate	359 (22.6)
Post-graduate education	425 (26.8)
Unknown	12 (0.8)
Covered by health insurance at V2, n (%)	
Yes	1489 (93.9)
No	96 (6.1)
Taking MVI or vitamin D at V2, n (%)	643 (40.8)
Vitamin use over observation period, n (%)	
Neither V2 nor V12	395 (24.9)
Discontinued after V2	124 (7.8)
Initiated after V2	539 (34.0)

Variable	Mean (SD) or n (%)
Both V2 and V12	519 (32.8)
Unknown	8 (0.5)
25(OH)D at V2 (nmol/L), mean (SD)	53.8 (24.3)
25(OH)D <50 nmol/L at V2, n (%)	683 (43.1)
25(OH)D ≤30 nmol/L at V2, n (%)	324 (20.4)

V2, Visit 2, GED, general education diploma; MVI, multivitamin; 25(OH)D, 25-hydroxyvitamin D.

Table 2:

Change in 25(OH)D between Visit 2 and Visit 12

	Visit 2 25(OH)D, Mean (SD)	Visit 12 25(OH)D, Mean (SD)	Δ25OHD Mean (SD)	p value for comparison of Δ25OHD
Entire cohort (nmol/L) Site [a,b]	53.8 (24.3)	70.0[C] (28.7)	16.2 (28.2)	--
Ann Arbor	41.9 (23.4)	58.5[C] (31.5)	16.6 (29.0)	
Boston	54.7 (25.9)	71.6[C] (27.8)	16.9 (28.1)	
Chicago	51.7 (27.1)	67.0[C] (26.5)	15.3 (28.0)	
UC Davis	55.6 (20.7)	72.7[C] (25.8)	17.1 (26.0)	0.7701
UC Los Angeles	63.4 (21.2)	77.3[C] (29.2)	13.9 (30.8)	
New Jersey	52.5 (20.4)	70.7[C] (27.4)	18.2 (28.6)	
Pittsburgh	53.7 (25.9)	70.2[C] (27.0)	16.5 (26.7)	
Race/ethnicity[a,b]				
Black	34.9 (18.7)	55.4[C] (28.8)	20.5 (26.5)	
White	63.5 (23.9)	76.6[C] (27.2)	13.1 (29.1)	
Chinese	49.3 (17.2)	70.5[C] (24.0)	21.1 (23.9)	**<0.001**
Hispanic	45.7 (16.4)	63.3[C] (25.8)	17.7 (25.5)	
Japanese	59.9 (18.9)	74.8[C] (28.6)	14.9 (31.1)	
Country of origin				
United States	54.1 (25.3)	70.3[C] (29.4)	16.2 (28.6)	0.800
Other	53.9 (19.9)	70.6[C] (25.9)	16.7 (26.6)	
Household income [a,b]				
<$20,000	44.5 (23.3)	58.6[C] (28.2)	14.1 (26.2)	
$20,000 to <$35,000	50.5 (25.8)	64.5[C] (29.2)	14.0 (27.8)	
$35,000 to <$50,000	50.8 (25.0)	66.9[C] (30.1)	16.1 (28.1)	0.378
$50,000 to <$75,000	53.8 (22.8)	72.1[C] (26.5)	18.2 (28.5)	
≥$75,000	59.3 (23.9)	74.9[C] (27.8)	15.7 (28.0)	
Language use				
Non-English language only	49.6 (17.4)	67.8[C] (28.1)	18.2 (25.8)	
English and non-English language	51.6 (18.8)	68.9[C] (25.2)	17.3 (26.9)	0.696
English language only	54.4 (25.4)	70.4[C] (29.3)	16.0 (28.6)	
Educational attainment [a,b]				
Less than high school	49.6 (19.2)	61.8[C] (24.4)	12.2 (23.0)	0.493

	Visit 2 25(OH)D, Mean (SD)	Visit 12 25(OH)D, Mean (SD)	Δ25OHD Mean (SD)	p value for comparison of Δ25OHD
Completed high school or GED	47.6 (23.7)	64.9[c] (29.5)	17.3 (29.4)	
Some college	51.4 (24.7)	68.5[c] (31.1)	17.1 (28.6)	
College graduate	57.8 (24.8)	72.5[c] (28.0)	14.6 (28.5)	
Post-graduate education	57.6 (23.6)	74.3[c] (26.0)	16.6 (27.9)	
Covered by health insurance at V2				
Yes	53.9 (24.4)	70.2[c] (28.7)	16.3 (28.5)	0.541
No	52.0 (23.9)	66.5[c] (28.3)	14.5 (24.7)	
Taking MVI or vitamin D at V2 [a,b]				
Yes	61.3 (24.1)	77.2[c] (27.5)	15.8 (28.2)	0.657
No	48.7 (23.2)	65.2[c] (28.6)	16.5 (28.3)	
Vitamin use over observation period [a,b]				
Neither V2 nor V12	44.1 (22.8)	48.4[c] (22.1)	4.3 (22.5)	
Discontinued after V2	53.4 (26.8)	55.3 (24.3)	1.9 (25.9)	
Initiated after V2	52.1 (22.9)	77.5[c] (26.6)	25.4 (28.8)	**<0.001**
Both V2 and V12	63.2 (23.1)	82.4[c] (25.5)	19.2 (27.8)	
Season of blood draw [a]				
Summer/winter	56.3 (23.3)	70.8[c] (14.5)	14.5 (29.8)	
Winter/summer	49.4 (23.7)	72.2[c] (27.6)	22.8 (26.6)	**<0.001**
Same season	54.1 (25.0)	68.6[c] (27.7)	14.5 (27.5)	
BMI category at V2 [a,b]				
Normal weight	61.1 (23.7)	77.7[c] (27.3)	16.6 (29.0)	0.693
Overweight	52.5 (24.1)	68.0[c] (27.7)	15.4 (27.7)	
Obese	40.4 (20.4)	57.3[c] (28.8)	16.9 (27.1)	

[a] p<0.001 among covariate levels at Visit 2,

[b] p<0.001 among covariate levels at Visit 12,

[c] p<0.001 at Visit 12 compared with Visit 2. 25(OH)D, 25-hydroxyvitamin D; Δ25(OH)D, change in 25-hydroxyvitamin D, GED, general education diploma

Table 3:

Predictors of 25(OH)D≤30 nmol/L at Visit 12 among women with 25(OH)D≤30 nmol/L at Visit 2

Variable	Overall p value for covariate	Odds ratio (95% CI)
Age (years)	0.763	0.98 (0.87-1.11)
BMI, kg/m^2, mean (SD)	0.425	1.02 (0.97-1.06)
Change in BMI (kg/m^2/year)	**0.033**	**1.11 (1.01-1.23)**
Race/ethnicity		
Black (n=196)		Reference
White (n=75)		**0.27 (0.11-0.66)**
Chinese (n=25)	**0.017**	0.42 (0.11-1.59)
Hispanic (n=14)		0.25 (0.04-1.46)
Japanese (n=14)		Unable to calculate
Household income		
<$20,000 (n=52)		Reference
$20,000 to <$35,000 (n=50)		2.06 (0.68-6.25)
$35,000 to <$50,000 (n=59)	0.203	1.71 (0.56-5.27)
$50,000 to <$75,000 (n=67)		0.69 (0.22-2.16)
≥$75,000 (n=75)		1.01 (0.30-3.41)
Educational attainment		
Less than high school (n=12)		Reference
Completed high school or GED (n=67)		0.35 (0.06-2.17)
Some college (n=117)	0.367	0.35 (0.06-2.08)
College graduate (n=52)		0.15 (0.02-1.10)
Post-graduate education (n=73)		0.29 (0.04-1.99)
Vitamin use over observation period, n (%)		
Neither V2 nor V12 (n=142)		Reference
Discontinued after V2 (n=32)	**<0.001**	1.63 (0.62-4.31)
Initiated after V2 (n=114)		**0.22 (0.10-0.49)**
Both V2 and V12 (n=35)		**0.17 (0.05-0.66)**
Visit 12 season		
Winter	**0.007**	Reference
Summer		**0.40 (0.21-0.78)**

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; GED, general education diploma. Note that no Japanese women had 25(OH)D≤30 nmol/L at Visit 12.