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Risk factors for vitamin D inadequacy among women with osteoporosis: an international epidemiological study

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SUMMARY

A serum 25-hydroxyvitamin D [25(OH)D] level of 75 nmol/l (30 ng/ml) has been proposed as the minimum for adequate vitamin D nutrition as lower levels are associated with increases in serum parathyroid hormone in otherwise healthy adults. Amongst 2589 community-dwelling, postmenopausal women with osteoporosis from 18 countries, recruited to determine risk factors for vitamin D inadequacy, 64% had vitamin D inadequacy. General health, education, ethnicity, sun exposure, skin reactivity, diet, recent travel to sunny climates, vitamin D supplementation, body mass index (BMI), season and latitude were assessed using logistic regression models. Asian ethnicity, BMI $\geq$30 kg/m^2, living in non-equatorial countries, inadequate vitamin D supplementation, poor/fair health, no education about vitamin D, skin reactivity and no recent travel to sunny areas were significant predictors. Several modifiable risk factors are associated with vitamin D inadequacy worldwide, suggesting potentially simple ways to increase vitamin D and improve bone health in postmenopausal women.

Keywords: 25-Hydroxyvitamin D; inadequacy; osteoporotic; postmenopausal; risk factors; vitamin D

INTRODUCTION

Vitamin D plays a major role in bone health. Vitamin D deficiency can lead to bone abnormalities such as rickets in children and osteomalacia in adults and suboptimal vitamin D status may cause decreased calcium absorption from the gut. As few foods provide a natural source of vitamin D and because fortification of foods is often unreliable (1,2), skin synthesis after sun exposure is thought to constitute the major source. However, the contribution of vitamin D production in the skin decreases with age (3) due to the reduction of substrate, 7-dehydrocholesterol, in skin and reduced sun exposure from elderly subjects.

Vitamin D may be especially important for women with osteoporosis to ensure adequate calcium absorption and optimise effects of pharmaceutical agents to treat osteoporosis.

A serum 25-hydroxyvitamin D [25(OH)D] level of 75 nmol/l[1] (or 30 ng/ml) has been proposed as the minimum for adequate vitamin D nutrition as lower levels are associated with increases in serum parathyroid hormone (PTH) in otherwise healthy adults (4). Many risk factors have been associated with vitamin D inadequacy. In the Longitudinal Aging Study Amsterdam, there was a strong inverse association between indices of total body fat, such as body mass index (BMI), and serum 25(OH)D levels in older men and women independent of age, gender, season, study region and smoking (5). Obesity is also associated with vitamin D insufficiency and secondary hyperparathyroidism (6). In a systematic review of studies reporting prevalence of vitamin D inadequacy among postmenopausal women with and without osteoporosis, the most commonly reported factors associated with inadequate vitamin D levels were low sun exposure, low dietary vitamin D intake (including supplements) and older age (7).

Given that sunshine exposure is the most important source of vitamin D, one should expect latitude (i.e. distance from the equator) to be an important risk factor for vitamin D inadequacy. This expected association was not observed in the international MORE study (8). In this study, it was argued that vitamin D levels between countries

[1]Conversion of ng/ml units to nmol/l can be accomplished by multiplying the reported serum 25(OH)D value in ng/ml by 2.5.

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may be overwhelmed by the influence of vitamin D fortification policies, dietary habits, time spent outdoors, clothing habits and skin type and pigmentation.

The objectives of this study were to describe the distribution of vitamin D levels, in a large group of postmenopausal women with osteoporosis from geographical areas at various latitudes and to examine the risk factors for vitamin D inadequacy including age, dietary consumption of vitamin D, levels of vitamin D supplementation, skin tone and sun exposure. The distribution of vitamin D levels, as measured by 25(OH)D, has been previously reported (9). Therefore, this paper will focus on assessing risk factors associated with vitamin D inadequacy. In this sample of postmenopausal women with osteoporosis, serum 25(OH)D levels >75 nmol/l were associated with maintenance of PTH in the stable range, while levels <75 nmol/l were associated with increasing PTH levels. These findings are consistent with other studies (8,10–13) and consistent with estimates obtained from expert opinion (4), thus providing a rationale for using the cut-off point of 25(OH)D <75 nmol/l for vitamin D inadequacy in these analyses.

METHODS

Study Design and Participants

This was a cross-sectional study of a convenience sample of women from Northern, Central and Southern Europe, the Middle East, Latin America, the Pacific Rim, and Asia who were receiving routine health care. Countries' latitudes varied from north to south of the equator (range 64N–38S). The sites within these countries were typical of medical outpatient practices treating postmenopausal women and included both general and specialist services. Participants were recruited either as they presented for routine medical care to the clinic or from a database of those attending the clinic. Medical charts for participants in the latter category were prescreened to confirm that participants had osteoporosis. Enrolment took place in two periods: period I (May 2004 to October 2004) and period II (November 2004 to March 2005).

Eligibility criteria were female gender, postmenopausal for at least 2 years (absence of menses, natural or surgical), and prevalent osteoporosis defined as one of the following: bone mineral density T-score ≤ -2.5 at any site or written documentation of diagnosed osteoporosis in the medical chart or a low trauma, non-pathological fragility fracture of the hip, spine, wrist, humerus or clavicle after age 45, or current or previous treatment for osteoporosis with any approved osteoporosis medication. Eligible patients provided written informed consent prior to participation in the study. All study protocols were in accord with the Declaration of Helsinki and were approved by Independent Ethics or Institutional Review Committees.

Information Collected

Data were collected at a single clinic visit. Height, weight, information regarding past medical history, current and prior medication use were collected. A survey was used to gather information on factors that can potentially influence serum 25(OH)D levels including dietary and supplemental vitamin D intake, weekly sun exposure, general health, discussion with the doctor about the importance of vitamin D in bone health and highest level of education. The section of the survey assessing the routine intake of vitamin D-rich foods was customised for each country to include a list of specific vitamin D-rich foods (e.g. fish) that were commonly eaten in that country. Finally, a single blood sample of 10–30 ml was collected, for assessment of serum 25(OH)D and serum intact PTH.

The primary outcome of interest, serum 25(OH)D level, was measured by the Nichols Advantage competitive binding chemiluminescence immunoassay [reference range 25–170 nmol/l (10–68 ng/ml), intra-assay precision 3.9% at 50.75 nmol/l (20.3 ng/ml), 3.0% at 124.8 nmol/l (49.9 ng/ml), and 3.6% at 144.5 nmol/l (57.8 ng/ml), lower limit of sensitivity 17.5 nmol/l (7 ng/ml); Quest Diagnostics Clinical Trials Laboratory Test Development Department, Van Nuys, CA, USA (14)].[1] Blood samples were transported using dry ice and picked up by the Quest Diagnostics courier from the local hub laboratories throughout the USA and transferred to their laboratory facility in California, where all samples were analysed.

Statistical Analysis

The population included all women with valid results for serum 25(OH)D. The distribution of serum 25(OH)D levels was calculated for each country, region and enrolment period as was the percentage of women with vitamin D inadequacy defined as serum 25(OH)D levels <75 nmol/l. In the northern hemisphere, summer was defined as May 2004 to October 2004 (enrolment period I), and winter was defined as November 2004 to March 2005 (enrolment period II), whereas in the southern hemisphere, it was the reverse. Data collected from equatorial regions (Thailand, Malaysia, Mexico and Brazil) were not assigned to specific seasons. For each potential risk factor, univariate logistic regression models were used to obtain the unadjusted odds ratio (OR) and corresponding 95% confidence interval for the relative risk of vitamin D inadequacy. $p \leq 0.05$ was considered statistically significant. Only risk factors with $p \leq 0.10$ were included in a multivariate stepwise logistic regression analysis. The final logistic regression model included only risk factors with $p \leq 0.05$. All statistical analyses were conducted using SAS Version 8.1 (SAS Institute, Cary, NC, USA).

RESULTS

Enrolment took place between May 2004 and March 2005 at 55 sites. Participating countries were grouped into five regions: Europe (Sweden, United Kingdom, Germany, The Netherlands, France, Switzerland, Hungary and Spain), the Middle East (Turkey and Lebanon), Asia (South Korea, Japan, Thailand and Malaysia), Latin America (Mexico, Brazil and Chile) and the Pacific Rim (Australia).

A total of 2606 women participated in the study, and serum 25(OH)D levels were available for 2589 (99.3%). Details of their characteristics have been reported elsewhere (9). In brief, women ranged in age from 41 to 96 years, with a mean age of 67.1 (± 7.7) years (Table 1). Over half the women were white, and most of the participants (63%) reported good to excellent health. Based on medical records, 2210 (85.4%) had a prior *T*-score <-2.5 at one or more skeletal sites. Most women ($n = 2010$, 77.6%) reported taking some form of treatment for osteoporosis, either pharmacological and/or calcium/vitamin D supplementation. As primary therapy, over half (59.8%, $n = 1548$) of participants were taking a bisphosphonate, selective oestrogen receptor modulator (raloxifene), calcitonin, hormone replacement therapy (HRT) or N-terminal PTH, with or without vitamin D supplementation. Some form of vitamin D and/or calcium was being taken as sole therapy in 461 (17.8%) of women while 579 women (22.4%) were untreated.

In the overall sample, the serum 25(OH)D level ranged from 17.5 to 607.5 nmol/l (7 to 243 ng/ml) with a mean of 67 nmol/l and SE = 0.8 (26.8 ng/ml and SE = 0.3). One woman had serum 25(OH)D level of 607.5 nmol/l (243 ng/ml) [next largest value was 300 nmol/l (120 ng/ml)]. Mean values for serum 25(OH)D by country and region are shown in Table 2 and ranged from a low of 44 nmol/l and SE = 1.8 (17.6 ng/ml and SE = 0.7) in South Korea to a high of 86.5 nmol/l and SE = 2.8 (34.6 ng/ml and SE = 1.1) in Sweden.

The percentages of women with serum 25(OH)D < 75 nmol/l by country and by enrolment period are displayed in Figure 1. In 11 of 14 non-equatorial countries, a slight to modest increase in the prevalence of vitamin D inadequacy was observed during winter. However, when season (winter vs. summer vs. no season) was evaluated as a risk factor in a univariate logistic regression model, there was no significant difference between summer and winter in the risk of vitamin D inadequacy; both conferred a similar elevated risk compared with 'no season' (equatorial region). Therefore, in subsequent analyses, winter and summer were combined into a single variable called 'non-equatorial' and compared with 'equatorial' (no season) countries.

Univariate logistic regression was used to determine factors associated with the prevalence of serum 25(OH)D levels <75 nmol/l (Table 3). Factors found to have a

Table 1 Characteristics of study participants

Participant characteristic	*n (%) or mean (SD)*
Age (years)	67.1 (7.7)
Range	41–96
Age category (years)	
<55	40 (1.5%)
55–60	555 (21.4%)
61–70	1145 (44.2%)
71–80	731 (28.2%)
81–90	115 (4.4%)
>90	3 (0.1%)
Race	
Asian	558 (21.6%)
Black	32 (1.2%)
White	1579 (61.0%)
Other*	420 (16.2%)
Body mass index (kg/m^2)	25.1 (4.5)
Education level	
University degree	331 (12.8%)
Secondary school	877 (33.9%)
Vocational school	386 (14.9%)
Primary school or less	992 (38.3%)
Missing	3 (0.1%)
BMD T-score <−2.5 at any site	2210 (85.4%)
Serum parathyroid hormone level (pg/ml)	30.7 (17.6)
History of fragility fracture	1310 (50.1%)
Sun exposure index†	
≥0.63	1160 (44.8%)
<0.63	1155 (44.6%)
Missing	274 (10.6%)
Self-reported health	
Excellent/very good	510 (19.7%)
Good	1128 (43.6%)
Fair/poor	950 (36.7%)
Missing	1 (0.0%)
Primary treatment for osteoporosis	
Prescription	
Bisphosphonates, SERM, calcitonin,	1549 (59.8)
PTH, oestrogen and/or progesterone with	
Calcium and vitamin D	398 (25.7)
Vitamin D2/D3 (only)	168 (10.8)
Calcium (only)	267 (17.2)
Active vitamin D analogue (alfacalcidol and calcitriol)	141 (9.1)
No other supplement	575 (37.1)
Other therapies only	461 (17.8)
Calcium and vitamin D	191 (41.4)
Vitamin D2/D3	99 (21.5)
Calcium	105 (22.8)
Active vitamin D analogue (alfacalcidol and calcitriol)	66 (14.3)
No osteoporosis therapy	579 (22.4)
Vitamin D supplementation‡	
Active analogue (alfacalcidol and calcitriol)	216 (13.6%)
Vitamin D2/D3	208(13.1%)
Vitamin D (unspecified)	467 (29.4%)
Calcium + vitamin D	696 (43.9%)

Table 1 (contd)

Participant characteristic	*n (%) or mean (SD)*
None	1186 (45.8%)
Vitamin D dose§	
≥400 IU	951 (36.7%)
<400 IU	452 (17.5%)
None	1186 (45.8%)

BMD, bone mineral density; SERM, selective oestrogen receptor modulator; PTH, parathyroid hormone. *Includes Hispanic, European and Multirace. †Calculated as number of hours per week spent outside without sun protection multiplied by percentage body part exposed to sunlight (9% for face, 1% for each hand, 9% for each arm, and 18% for each leg). A sun index of 0.64, for example, corresponds to having arms, face and hands exposed to the sun without protection for 2.2 h a week. ‡Women could belong to multiple categories. §Does not include active vitamin D.

significant ($p < 0.05$) association with vitamin D inadequacy were race (Asian and other), higher BMI (>30 kg/m^2), latitude of enrolment country (non-equatorial), vitamin D supplementation (<400 IU daily and none), poor general health, absence of discussion with a doctor regarding the importance of vitamin D to bone health, lower education level, less sun exposure, darker skin tones, tanning with difficulty, and absence of travel to sunny areas in the past month.

All the above factors, except for education level, sun exposure and skin tone, remained significantly associated with vitamin D inadequacy when included in a multivariate analysis. The estimated odd ratios in the multivariate analyses were similar to those seen in the univariate analysis (Figure 2).

DISCUSSION

Despite the widely recognised importance of vitamin D in the management of bone health, low levels of serum 25(OH)D were observed among the 2589 postmenopausal women who participated in this study. Worldwide, approximately 64% of postmenopausal women with osteoporosis had serum 25(OH)D levels <75 nmol/l. None of the regions had average serum 25(OH)D level >75 nmol/l; however, within these regions the prevalence of inadequacy varied among countries independent of latitude, suggesting that factors other than latitude influence vitamin D levels in this sample of osteoporotic women.

Among the potential risk factors identified in this study, race, high BMI, living in non-equatorial regions, vitamin D supplementation <400 IU daily, poor general health, absence of discussion with a doctor regarding the importance of vitamin D to bone health, low education level, low sun exposure, skin reactivity and absence of travel to sunny areas in the past month were associated with vitamin D inadequacy defined as serum 25(OH)D levels <75 nmol/l.

Our findings of BMI being strongly associated with vitamin D inadequacy are consistent with several other reports (5,6,15). It is not clear whether this relates to diminished

Table 2 Mean levels of serum 25-hydroxyvitamin D nmol/l (ng/ml) by country and latitude

		Serum 25(OH)D nmol/l (ng/ml)	
Country/region (n)	*Latitude*	*Mean*	*SE*
Europe (1020)		73.3 (29.3)	1.3 (0.5)
Sweden (150)	64–58°N	86.5 (34.6)	2.8 (1.1)
United Kingdom (98)	53–52°N	58.5 (23.4)	3.3 (1.3)
Germany (100)	53–48°N	66.8 (26.7)	3.5 (1.4)
The Netherlands (50)	51°N	77.0 (30.8)	4.8 (1.9)
France (199)	50–46°N	70.5 (28.2)	3.8 (1.5)
Switzerland (173)	47–46°N	77.3 (30.9)	2.3 (0.9)
Hungary (100)	47°N	78.3 (31.3)	3.8 (1.5)
Spain (150)	43–38°N	68.0 (27.2)	2.8 (1.1)
Middle East (401)		51.0 (20.4)	1.3 (0.5)
Turkey (150)	41–38°N	54.5 (21.8)	2.5 (1.0)
Lebanon (251)	34°N	48.8 (19.5)	1.5 (0.6)
Asia (549)		61.0 (24.4)	1.0 (0.4)
South Korea (101)	38°N	44.0 (17.6)	1.8 (0.7)
Japan (198)	36–35°N	51.5 (20.6)	1.0 (0.4)
Thailand (100)	13°N	75.8 (30.3)	2.5 (1.0)
Malaysia (150)	5–3°N	75.5 (30.2)	2.0 (0.8)
Latin America (415)		74.0 (29.6)	1.5 (0.6)
Mexico (149)	19°N	65.5 (26.2)	2.3 (0.9)
Brazil (151)	13–25°S	81.5 (32.6)	2.5 (1.0)
Chile (115)	34°S	75.5 (30.2)	3.0 (1.2)
Pacific Rim (204)		70.0 (28.0)	2.0 (0.8)
Australia (204)	31–37°S	70.0 (28.0)	2.0 (0.8)
All counties (2589)		67.0 (26.8)	0.8 (0.3)

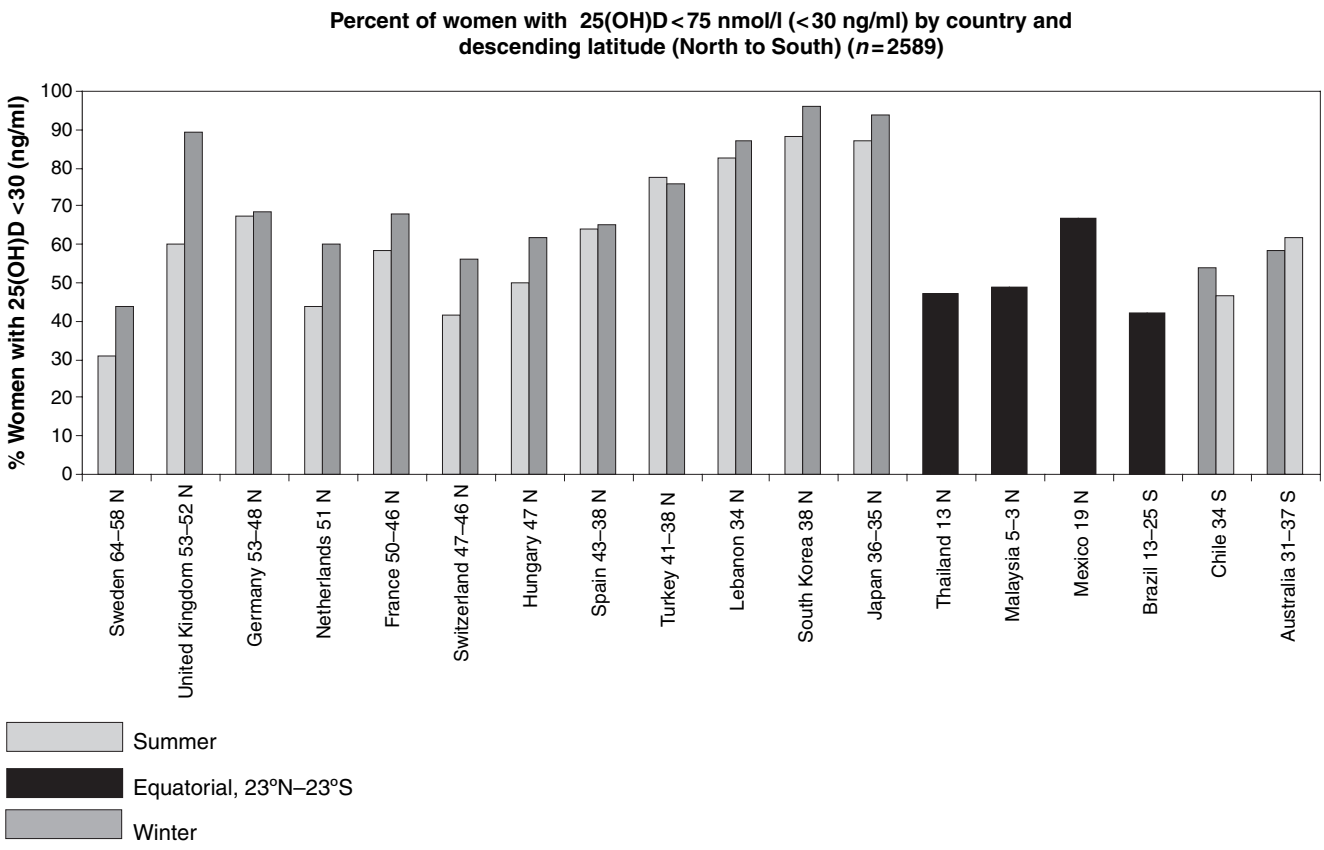

Figure 1 Vitamin D inadequacy by country. Countries in the equatorial region were allowed to enroll subjects year-round as they do not have distinct seasons

sun exposure or to decreased bioavailability of vitamin D in excessive fat stores.

Though a slight to modest increase in the prevalence of vitamin D inadequacy was observed during the winter in most of the non-equatorial countries, season itself was not a significant predictor of vitamin D inadequacy. Women living in countries with latitudes $>23°$ were at greater risk of vitamin D inadequacy than those living in countries closer to the equator, but winter season was not significantly associated with vitamin D inadequacy in the non-equatorial countries. This suggests that vitamin D inadequacy among postmenopausal women with osteoporosis is not just a winter phenomenon.

The dietary intake questionnaire was adapted for each country to include commonly consumed vitamin D-rich foods, including fatty fish. However, fish consumption was relatively low among women in this study across all countries and only number of servings was recorded and not quantity consumed. Thus it was not possible to examine the potential impact of very high fish consumption on vitamin D levels. In addition to the factors noted above, it was expected that clothing and cultural habits may strongly influence the effect of sun exposure in some countries, accounting for the variability in prevalence of vitamin D inadequacy among countries at similar latitude.

This study has some limitations. Sites were instructed to recruit a broad community-based sample that would be typical of postmenopausal women with osteoporosis seeking routine health care in that country. However, this sample cannot be considered population based and therefore findings may not be generalisable to all postmenopausal women with or without osteoporosis. Some race and latitude differences are collinear so it is difficult to determine which factor may be primary and secondary. However, these effects were modest and did not alter the overall high prevalence of vitamin D inadequacy. Moreover, commercial assays such as Nichols Advantage have been criticised for incorrectly estimating serum 25(OH)D levels when compared with a gold standard high-performance liquid chromatography (HPLC), i.e. overestimation of 25-$(OH)D_3$ (16,17) and underestimation of 25-$(OH)D_2$ (17,18). However, results using Nichols Advantage and HPLC in a sample of postmenopausal osteoporotic women were almost identical for the prevalence of vitamin D inadequacy (10), suggesting that estimates of prevalence in this population are reasonable. Finally, our study was amongst individuals seeking health care for osteoporosis and thus may be more conscious about their health compared with the general population. This could contribute to the overall prevalence of vitamin D insufficiency (8).

Table 3 Risk factors for vitamin D inadequacy (values from univariate regression)

		Univariate	
Risk factor	*n (%)*	*Odds ratio (95% CI)*	*p-value*
Age			
≤70 years	1740 (67.2)	Ref	
>70 years	849 (32.8)	1.14 (0.96–1.35)	0.140
Race			
White	1579 (61.0)	Ref	
Asian	558 (21.6)	1.60 (1.30–1.97)	<0.001
Other	452 (17.5)	1.14 (0.92–1.42)	0.359
BMI			
≤30 kg/m^2	2233 (86.2)	Ref	
>30 kg/m^2	356 (13.8)	2.40 (1.83–3.14)	<0.0001
Latitude			
Equatorial	550 (21.2)	Ref	
Non-equatorial	2039 (78.8)	1.91 (1.58–2.32)	<0.0001
Significant medical history*			
Yes	73 (2.8)	1.02 (0.63–1.67)	
No	2516 (97.2)	Ref	0.923
Significant concomitant medication†			
Yes	224 (8.7)	1.24 (0.93–1.67)	
No	2365 (91.3)	Ref	0.147
Vitamin D supplements			
≥400 IU daily	951 (36.7)	Ref	
<400 IU daily	452 (17.5)	1.78 (1.41–2.24)	0.018
No supplement	1186 (45.8)	2.36 (1.97–2.82)	<0.0001
General health			
Excellent/very good	510 (19.7)	Ref	
Good	1128 (43.6)	1.22 (0.99–1.51)	0.191
Fair/poor	950 (36.7)	1.86 (1.49–2.33)	<0.0001
Discussed vitamin D with doctor			
Yes	1403 (54.2)	Ref	
No	1180 (45.6)	1.55 (1.31–1.82)	<0.0001
Education level			
High school or less	1869 (72.2)	1.38 (1.15–1.64)	
University	717 (27.7)	Ref	<0.0001
Sun exposure index groups‡			
≤0.63	1160 (44.8)	1.12 (0.99–1.40)	
>0.63	1155 (44.6)	Ref	0.059
Skin tone			
Light	947 (36.6)	Ref	
Medium	1317 (50.9)	0.68 (0.52–0.89)	>0.0001
Dark	289 (11.2)	1.24 (1.04–1.48)	>0.0001
Skin reaction			
Difficulty tanning	941 (36.6)	1.63 (0.98–1.38)	
Tanning easily	1638 (63.3)	Ref	0.078
Travel to sunny areas			
Yes	559 (21.6)	Ref	
No	2030 (74.4)	1.86 (1.54–2.25)	<0.0001
Consumption of vitamin D-rich foods§ (based on median split)			
<5 time per month	919 (35.5)	0.89 (0.74–1.06)	
≥5 times per month	1126 (43.5)	Ref	0.192

BMI, body mass index. *Includes gastric surgery, chronic liver diseases, chronic renal diseases, malabsorptions, morbid obesity, hyperparathyroidism, chronic granulomatous diseases, and/or malnutrition. †Concomitant use of glucocorticoids, anticonvulsants and/or antimycobacterials. ‡Sun index calculated using the number of hours per week spent outside without sun protection multiplied by the percentage of the body parts exposed to sunlight (9% for the face, 1% for each hand, 9% for each arm, and 18% for each leg). A sun index of 0.63, for example, corresponds to having arms, legs and hands exposed to the sun without protection for 2.2 h a week. §Determined as the number of times vitamin D-rich foods were consumed in the past month.

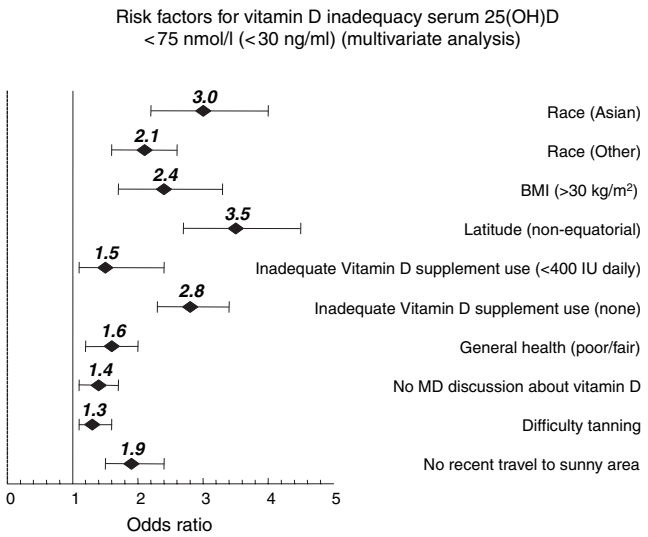

Figure 2 Results of multivariate logistic regression

Several important and clinically relevant conclusions can be drawn from this study. Among postmenopausal women with osteoporosis, even in countries with ample sunlight, vitamin D inadequacy is common with 64% of postmenopausal women in this 18-country study having vitamin D inadequacy. The potential adverse effects of vitamin D inadequacy, particularly on bone health, and its high prevalence suggest that modifiable risk factors such as high BMI, inadequate vitamin D supplementation, limited education about the importance of vitamin D and low sun exposure, could reasonably be targeted as part of a comprehensive strategy to improve bone health in postmenopausal women.

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