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Original research

Simple prediction model for vitamin D deficiency in women with osteoporosis or risk factors for osteoporosis in Thailand

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ABSTRACT

Introduction: In Thailand, the assessment of vitamin D status by measuring 25-hydroxyvitamin D[25(OH)D] levels in individuals at risk for osteoporosis is constrained by limited facilities and high costs. This study aimed to create a clinical model for predicting vitamin D deficiency in women with osteoporosis or risk factors for osteoporosis.
Materials and Methods: This was a cross-sectional study of 490 women. All participants had 25(OH)D levels measured. A questionnaire was used to assess factors related to vitamin D status. Vitamin D deficiency was defined as 25(OH)D levels < 30 ng/mL. Logistic regression analyses were conducted to investigate predictors of vitamin D deficiency. In the model, odds ratios (ORs) were converted into simple scores. The optimal cutoff for women at a high risk of vitamin D deficiency was established. Internal validation was assessed using a Bootstrap.
Results: Sixty percent had vitamin D deficiency. The final model for predicting vitamin D deficiency consisted of a body mass index ≥ 25 kg/m^2 (OR:1.15), lack of exercise (OR:1.59), exercise 1–2 times/week (OR:1.40), sunlight exposure < 15 min/day (OR:1.70), no vitamin D supplementation (OR:8.76), and vitamin D supplementation of 1–20,000 IU/week (OR:2.31). The area under the curve was 0.747. At a cutoff of 6.6 in total risk score (range 4–13.6), the model predicted vitamin D deficiency with a sensitivity of 71.9 % and a specificity of 65.3 %. The internal validation by Bootstrap revealed a ROC of 0.737.
Conclusions: In women at risk of osteoporosis, a simple risk score can identify individuals with a high risk of vitamin D deficiency. These women could benefit from vitamin D supplementation without requiring 25(OH)D measurements.

Introduction

Vitamin D is essential as a non-pharmacological treatment for osteoporosis [1], as it is crucial for normal bone development and maintenance of bone health. Optimal vitamin D status plays a significant role in improving muscle performance [2,3], reducing the risk of falls [4] and fracture [5,6], and enhancing the response to antiresorptive drugs [6,7]. Vitamin D3 (cholecalciferol) is produced through sunlight (UVB) exposure on the skin. Typically, exposing the hands, face, and arms to sunlight for 10 to 15 min per day between 10 AM and 3 PM is adequate for vitamin D synthesis in most individuals [8]. However, the factors affecting vitamin D synthesis depend on the exposure time, duration of exposure, location in the world, aging, sun protection, religion, lifestyle, and color of the skin [9]. The dietary intake encompasses both vitamin D_3 and vitamin D_2 (ergocalciferol), a molecular derivative of plant origin. Only a few food items naturally contain vitamin D, such as oily fish, salmon, sardines, mackerel, eggs, liver, and fortified foods [10]. Therefore, supplementation may be necessary to restore adequate levels

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in cases of vitamin D deficiency.

The vitamin D status is determined by assessing the major circulating metabolite of vitamin D known as 25-hydroxyvitamin D [25(OH)D]. These levels depend on several factors, including genetics, factors related to sun exposure, body mass index (BMI), sex, age level of physical activity, food fortification with vitamin D, and use of vitamin D supplementation [11]. For example, a recent study reported that the most significant predictors for low 25(OH)D levels were ambient ultraviolet radiation and total intake of vitamin D. In addition, low physical activity, less time spent outdoors, high BMI, living alone, poor quality of life, or smoking were also associated with vitamin D deficiency [12].

Although there is no universal cutoff for 25(OH)D levels, it is generally accepted that levels of < 30 ng/mL indicate vitamin D deficiency, particularly in individuals at risk for osteoporosis [1,13,14]. Increasing evidence has been suggested that vitamin D deficiency is currently a global public health problem and is prevalent in Thailand, particularly among older people at risk of osteoporosis. Studies have shown that the prevalence of vitamin D deficiency (25(OH)D levels $<$ 30 ng/mL) in older Thai people ranges from 34.3 % to 69.1 % [15,16]. However, clinical characteristics predictive of vitamin D deficiency in this high-risk group have not been extensively studied in Thailand. 25(OH)D measurement is generally recommended in people with a high risk of vitamin D deficiency, such as those with osteoporosis [1,13,14]. However, due to limited facilities and high costs, measuring 25(OH)D levels in all at-risk individuals in Thailand is not feasible.

To address this, our study aimed to investigate predictors for vitamin D deficiency in women with osteoporosis or risk factors for osteoporosis using a questionnaire and create a clinical model for predicting vitamin D deficiency.

Methods

Study design and participants

This cross-sectional study was conducted at the outpatient clinic of the Internal Medicine Department, Obstetrics and Gynecology Department, and Orthopedic Department at Ramathibodi Hospital. These clinics were the main departments caring for osteoporosis. The recruitment phase was prolonged between August 2016 and August 2019 due to a lower-than-expected recruitment rate and insufficient study coordinators. The inclusion criteria were women aged > 40 years since we would like to include as many participants as possible. This would allow us to include some women with premature menopause (menopause before age 45) and women in the menopause transition. We included participants who were initially evaluated for osteoporosis or followed up for osteoporosis and had 25(OH)D levels measured at the central laboratory of Ramathibodi Hospital within 2 weeks before or after the recruitment. The exclusion criteria were unwilling participants. Participants were also excluded when they had pre-existing conditions that could independently affect bone health, for example, hyperparathyroidism, hypercalcemia, Cushing's disease, bone metastasis, and Paget's disease. About 20 % of screened participants in this cohort declined to recruit to the study. The main reason for not being willing to be recruited was that they did not have time to respond to the questionnaire. Those participants were followed as usual by their physicians. All included participants provided written informed consent. The Institutional Review Board, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2023/894) approved the protocol.

Body weight (previously assessed using a calibrated electronic scale with an accuracy of 0.01 kg) and height (previously assessed using a wall-mounted stadiometer with a standard method and barefoot) data were extracted from medical records. The BMI was calculated using the standard following formula: [weight (kg)/height $(m)^2$]. Age, current medications, and underlying diseases were also extracted from the medical records. Well-trained study coordinators took responsibility for reviewing the medical records.

Bone mineral density (BMD) was assessed by dual-energy x-ray absorptiometry (DXA) at the Radiology Department, Ramathibodi Hospital. As previously reported [17], each subject changed into light clothing before undergoing BMD assessment by DXA at the lumbar spine (L1–L4 vertebrae) and hip (total hip and femoral neck). Using the fast-array mode, all measurement procedures were performed following the International Society for Clinical Densitometry recommendations [18]. The measurements were taken by the International Society for Clinical Densitometry-certified densitometry technologists using a Hologic Discovery DXA scanner (Hologic, Marlborough, MA). Quality assurance was maintained by daily calibration and the use of one phantom. The precision error in BMD was calculated as root mean square (RMS) averages of the standard deviations of repeated measurements. The RMS values of lumbar spine and femoral neck were 0.006 and 0.012 g/cm^2, respectively.

An osteoporotic fracture was defined as having a low-trauma (i.e., fragility) fracture or asymptomatic vertebral fracture detected by vertebral fracture assessment or plain film. Osteoporosis was defined as a BMD T-score ≤ -2.5. A BMD Z-score of < -2 in premenopausal women was defined as low bone mass, and a BMD T-score between -1.0 and -2.5 in postmenopausal women was defined as osteopenia [1]. Some participants visited the osteoporosis clinic for the first time. Therefore, the BMD results of some of the participants were unavailable.

Assessment of risk factors for vitamin D deficiency

Each participant completed a questionnaire designed to quantify vitamin D intake through diet and sun exposure and record the conditions or medications that affect vitamin D storage/metabolism (Table 1). This questionnaire was modified from that used in a study by Bolek-Berquist et al. [19]. In brief, factors associated with 25(OH)D levels in Thai people, including age and living area, were added to the questionnaire [15]. In addition, few Thai people perform suntanning. Therefore, the related question was removed. However, it's important to note that this modified version has never been validated in Thais.

We obtained data on the season in which participants entered the study, daily sunlight exposure in the last week in minutes between 10 AM and 3 PM, exercises, sunscreen use, and the current medical status, including supplemental vitamin D intake. At the time of conducting the study, summer was from March to May, the rainy season was from June to October, and winter was from November to March, according to the data from the Thai Meteorological Department. Applying sunscreen to any of the following areas: face, body, or both face and body was classified as yes. The interview was performed directly at the outpatient clinic or by a phone call within 4 weeks after 25(OH)D levels measurement to avoid recall bias. The interview took approximately 5 min to complete. When the participants were unable to communicate (e.g., they had stroke or hearing loss), we interviewed their caregivers instead.

25(OH)D measurement

According to the recommendation of the Endocrine Society clinical practice guideline [14], and the Thai Osteoporosis Foundation [13], vitamin D deficiency in individuals at risk for osteoporosis is defined as having 25(OH)D levels < 30 ng/mL. 25(OH)D levels ≥ 30 ng/mL is defined as vitamin D sufficiency. Serum 25(OH)D levels were measured using a chemiluminescence immunoassay (Liaison; DiaSorin Inc.; Stillwater, MN) performed at the central laboratory of Ramathibodi Hospital as routine practice. The reported total between-run coefficients of variation for the serum samples ranged from 10.8 % to 12.6 %.

Statistical analysis

The variables that had missing data were the season of blood drawn (missing n = 6), occupation (missing n = 1), exercise (missing n = 1),

Table 1
The vitamin D questionnaire.

Date	season		
Age	years	months	
Weight	kg	Height cm	BMI kg/m^2
Menopausal status	1. Premenopausal woman	2. Postmenopausal woman	
Occupation			
Living area	1. Bangkok	2. Urban area	3. Rural area
Education	1. Undergraduate	2. Primary school	3. High school
	4. Bachelor	5. Master's degree	6. Doctor's degree
25(OH)D levels	……ng/mL date……		
	Indication for testing:		
	1. Osteoporosis/osteopenia/low bone mass		
	2. Glucocorticoid induced osteoporosis		
	3. Others specify…….….....		
Exercise	1. Lack of exercise	2. 1—2 times/week	3. ≥ 3 times/week
Sunscreen Use	1. No	2. Yes	
Sunlight exposure between 10.00—15.00 in the last week	1. < 15 min/day	2. ≥ 15 min/day	
Drink milk	1. No	2.Yes	
Calcium supplements	1. No	2. Yes	
	Brand…….….....	elemental Ca…….…..mg/tab	
	Total elemental Ca…….mg/day		
Vitamin D supplements	1. No	2. Yes	
	Brand…….….....	dose……IU/tab	
	Total vitamin D dose ……IU/week		
Cod liver or fish oil supplements	1. No	2. Yes brand…….….....	
Diseases that affect vitamin D metabolism	1. No		
	2. Cirrhosis		
	3. Chronic kidney disease stage 3 or over		
	4. Dermatologic diseases that are sensitive to sunlight		
	5. Eating disorders		
	6. Inflammatory bowel disease		
	7. Chronic diarrhea		
	8. Others specify…….….....		
Drugs that affect vitamin D metabolism	1. No		
	2. Antiepileptic		
	3. Steroids		
	4. Others specify……		
Use anti-osteoporotic drugs	1. No	2. Yes	
Bone mineral density (BMD) results	1. No result		
	2. Normal		
	3. Low bone mass (premenopausal women)		
	4. Osteopenia		
	5. Osteoporosis		
	6. Osteoporotic fracture		

and no cod liver or fish oil (missing n = 5). Missing values were excluded from the analysis, and results were based on the number of non-missing values.

The mean and standard deviation (SD) were used to describe continuous variables if data were normally distributed. The median and interquartile range (IQR) were used for non-continuous variables. The frequency and percentage were used to describe categorical data. Continuous variables were stratified into the following categories according to a BMI < 25 vs. ≥ 25 kg/m^2 using the threshold values for obesity in Thailand [20]. Vitamin D_2 20,000 IU is the only prescription form available in Thailand. Therefore, we hypothesized that differences in the amount of vitamin D supplementation can predict vitamin D deficiency with varying magnitudes. Consequently, we divided vitamin D supplementation into three groups: no supplementation, 1–20,000 IU/week, and > 20,000 IU/week.

Logistic regression analyses were performed to examine the predictors of vitamin D deficiency. Predictors with p-values less than 0.1 in the univariate logistic regression analysis were considered in a multivariate analysis. The forward selection method was used to select the most parsimonious model. Next, we generated the vitamin D deficiency score using odds ratios (ORs) from multivariate analysis. To ease calculation, the OR values of each predictor were rounded to the nearest 0.1. For example, an OR of 1.59 would be rounded as 1.6. The attributed points were then summed up for each participant. A higher score indicated a higher risk of vitamin D deficiency. To examine the discriminative capacity, we performed a receiver operating characteristic (ROC) analysis, and we used the Hosmer–Lemeshow test for goodness-of-fit to examine calibration performance. The sensitivity, specificity, and positive and negative predictive values of the different cutoffs in the total risk score were calculated. A positive likelihood ratio (LR +) was used to calibrate the cutoff for individuals at high risk of vitamin D deficiency. Internal validation of this model was carried out using a bootstrap resampling method of 1000. The area under the ROC curve, calibration slope, and Brier were estimated to indicate the model performance of internal validation. We completed the analysis using Stata version 14.1, and the statistical significance was set at $p < 0.05$.

Results

A total of 490 individuals (Internal Medicine Department: n = 322 [65.7 %], Obstetrics and Gynecology Department: n = 153 [31.2 %], and Orthopedic Department: n = 12 [3.1 %]) participated in this study. The mean age and mean BMI were 67.2 ± 10 years and 24.3 ± 4.2 kg/m^2, respectively. The mean 25(OH)D concentration was 29.2 ± 11.3 ng/mL, and 60 % of the participants had vitamin D deficiency (25(OH)D levels < 30 ng/mL, vitamin D deficiency group). The majority of the participants were unemployed or retired and lived in Bangkok. In this cohort, 44.7 %, 36.1 %, and 19.2 % of the participants had no vitamin D supplementation, 1–20,000 IU/day, and > 20,000 IU/day, respectively. According to the BMD results, 184 of the participants had low bone mass/osteopenia, and 180 of them had osteoporosis or an osteoporotic fracture.

The clinical characteristics of the participants stratified by the vitamin D status are shown in Table 2. The participants in the vitamin D deficiency group had a higher BMI than those in the vitamin D sufficiency group ($p = 0.006$). The participants in the vitamin D deficiency group were more likely to not exercise than those in the vitamin D sufficiency group ($p = 0.055$). A lower proportion of participants in the vitamin D deficiency group used sunscreen ($p = 0.022$), while a higher proportion of them had sunlight exposure < 15 min/day ($p = 0.005$) than those in the vitamin D sufficiency group. A higher proportion of participants in the vitamin D deficiency group did not receive calcium ($p < 0.001$) or vitamin D supplementation ($p < 0.001$) than those in the vitamin D sufficiency group. Osteopenia/osteoporosis was less prevalent in the vitamin D deficiency group than in the vitamin D sufficiency group (69.7 % vs. 81.1 %, $p = 0.012$).

The univariate analysis showed that blood drawn in the summer, a BMI ≥ 25 kg/m^2, lack of exercise, lack of sunscreen use, sunlight exposure < 15 min/day, no calcium supplementation, and no vitamin D supplementation were associated with vitamin D deficiency (Table 3). No vitamin D supplementation showed the highest OR for vitamin D deficiency (OR: 5.64, 95 % confidence interval [CI] 3.72–8.55). In the analysis of the different vitamin D dosage groups, no vitamin D supplementation and 1–20,000 IU/week were associated with vitamin D deficiency, with ORs of 8.73 and 2.11, respectively. We found an association between vitamin D and calcium supplementations. Thus, it is unsuitable to include both variables simultaneously in the multivariate model. We included vitamin D supplementation in the multivariate model because it was more clinically meaningful than calcium supplementation (higher odd ratios).

The multivariate analysis was performed to investigate the significant predictors of vitamin D deficiency (Table 3). Significant predictors were a BMI ≥ 25 kg/m^2 (OR: 1.15, 95 % CI 0.99–2.30), lack of exercise (OR: 1.59, 95 % CI 1.02–2.49), exercise 1–2 times/week (OR: 1.40, 95 % CI 0.79–2.46), sunlight exposure < 15 min/day (OR: 1.70, 95 % CI 1.04–2.78), no vitamin D supplementation (OR: 8.76, 95 % CI 5.02–15.28), and vitamin D supplementation of 1–20,000 IU/week (OR: 2.31, 95 % CI 1.34–3.96). To simplify clinical application, the ORs of the predictors were further converted into simple scores in the vitamin D deficiency prediction model.

The final model (n = 488) for predicting vitamin D deficiency is shown in Table 4. The ROC analysis showed an area under the curve of 0.747 (95 % CI 0.703–0.791). The Hosmer–Lemeshow goodness-of-fit test for the multiple logistic regression was non-significant ($p = 0.204$), which indicated that the model fit the data well. A cutoff of 6.6 with LR+ = 2 was the optimum cutoff value for predicting vitamin D deficiency, with a sensitivity of 71.9 % and a specificity of 65.3 % (Table 5). The internal validation by the bootstrap method with 1000 replications showed an area under the ROC curve of 0.737 (95 % CI 0.694–0.781). The calibration slope was 0.945 (95 % CI 0.764–1.175), which is close to 1, suggesting good calibration. The Brier scale was 0.159, which showed high model prediction accuracy and was close to the actual outcome.

Table 2
Descriptive characteristics of participants stratified by vitamin D status (n = 490).

Characteristics	Vitamin D sufficiency group n = 196	Vitamin D deficiency group n = 294	*p* value
25(OH)D levels, ng/mL	40.3 ± 8.7	21.8 ± 5.1	
Demographic data			
Season of blood drawn[a], n (%)			**0.087**
Summer (n = 68)	20 (10.4)	48 (16.4)	
Rainy (n = 251)	98 (51.1)	153 (52.4)	
Winter (n = 165)	74 (38.5)	91 (31.2)	
Age (years)	67.3 ± 9.4	67.2 ± 10.2	0.963
BMI (kg/m^2)	23.7 ± 4.0	24.7 ± 4.3	**0.006**
BMI categories, n (%)			**0.004**
BMI < 25 kg/m^2	136 (69.4)	166 (56.5)	
BMI ≥ 25 kg/m^2	60 (30.6)	128 (43.5)	
Occupation[b], n (%)			0.639
Outdoor	6 (3.1)	7 (20.4)	
Indoor, unemployed/retried	189 (96.9)	287 (97.6)	
Living area, n (%)			0.850
Bangkok	121 (61.7)	180 (61.2)	
Not Bangkok			
Urban	36 (18.4)	50 (17)	
Rural	39 (19.9)	64 (21.8)	
Education, n (%)			0.658
Below bachelor's degree	92 (46.9)	144 (49)	
Bachelor's degree or above	104 (53.1)	150 (51)	
Exercise[b], n (%)			**0.055**
Lack of exercise	77 (39.3)	145 (49.5)	
1–2 times/week	37 (18.9)	54 (18.4)	
≥3 times/week	82 (41.8)	94 (32.1)	
Sunscreen use, n (%)	93 (47.4)	109 (37.1)	**0.022**
Sunlight exposure (10.00–15.00)[b], n (%)			
<15 min/day	144 (73.5)	246 (84)	**0.005**
≥15 min/day	52 (26.5)	47 (16)	
No consumption of milk, n (%)	105 (53.6)	162 (55.1)	0.739
Calcium supplementation			
No, n (%)	38 (19.4)	118 (40.1)	**<0.001**
Dose (mg/day)**	600 (240–1200)	490 (0–600)	**<0.001**
Vitamin D supplementation			
No, n (%)	43 (21.9)	176 (59.9)	**<0.001**
Dose (IU/wk)**	20,000 (7,000–40,000)	0 (0–20,000)	**<0.001**
Vitamin D dosage categories, n (%)			
0 IU/week	43 (21.9)	176 (59.9)	**<0.001**
1–20,000 IU/week	89 (45.4)	88 (29.9)	
>20,000 IU/week	64 (32.7)	30 (10.2)	
No cod liver or fish oil supplementation[c], n (%)	195 (91.8)	276 (95.2)	0.130
Has diseases that affect vitamin D metabolism, n (%)	10 (5.1)	19 (6.5)	0.532
Use of drugs that affect vitamin D metabolism, n (%)	7 (3.6)	14 (4.8)	0.524
Not using anti-osteoporotic drugs, n (%)	154 (78.6)	249 (84.7)	0.082
BMD categories, n (%)			**0.012**
No result	20 (10.2)	67 (22.8)	
Normal	17 (8.7)	22 (7.5)	
Low bone mass	2 (1)	1 (0.3)	
Osteopenia	74 (37.8)	107 (36.4)	
Osteoporosis	80 (40.8)	92 (31.3)	
Osteoporosis fracture	3 (1.5)	5 (1.7)	

** = IQR.
BMI = body mass index; n = number.
[a] n = 484; [b] n = 489; [c] n = 485.

Discussion

In this study of Thai women with osteoporosis or risk factors for osteoporosis who visited the outpatient clinic of a tertiary center hospital, the prevalence of vitamin D deficiency [25(OH)D < 30 ng/ml] was 60 %. A comprehensive interview conducted via a questionnaire can serve as an initial tool for identifying women at high or low risk of vitamin D deficiency. The questionnaire identified four independent and significant variables that predicted vitamin D deficiency, including BMI, exercise, sunlight exposure, and dosage of vitamin D supplementation. A score of ≥ 6.6 predicted vitamin D deficiency with a sensitivity of 71.9 % and a positive predictive value of 75.5 %. This model performed well in internal validation, with an area under the ROC curve of 0.737 using Bootstrap. This is the first study in Thailand to develop a simple

Table 3
Univariate and multivariate odds ratios for vitamin D deficiency [25(OH)D < 30 ng/mL].

	Univariate model Odd ratio (95 % CI)	*p* value	Multivariate model Odd ratio (95 % CI)	*p* value
Season of blood drawn[a]				
Rainy	1.27 (0.85,1.89)	0.240		
Summer	1.95 (1.07,3.57)	0.030		
Winter	1			
BMI ≥ 25 kg/m^2	1.74 (1.19,2.56)	0.004	1.15 (0.99,2.30)	0.054
Exercise[b]				
Lack of exercise	1.64 (1.10,2.46)	0.016	1.59 (1.02,2.49)	0.043
1–2 times/week	1.27 (0.76,2.13)	0.356	1.40 (0.79,2.46)	0.245
≥3 times/week	1		1	
Lack of sunscreen use	1.53 (1.06,2.21)	0.023		
Sunlight exposure < 15 min/day	1.89 (1.21,2.95)	0.005	1.70 (1.04,2.78)	0.034
No calcium supplementation	2.79 (1.82,4.26)	<0.001		
No vitamin D supplementation	5.64 (3.72,8.55)	<0.001		
Vitamin D dosage categories				
0 IU/week	8.73 (5.05,15.09	<0.001	8.76 (5.02,15.28)	<0.001
1–20,000 IU/week	2.11 (1.25,3.56)	0.005	2.31 (1.34,3.96)	0.002
>20,000 IU/week	1		1	

BMI = body mass index;
[a] n = 484; [b] n = 489.

Table 4
Final model to predict vitamin D deficiency [25(OH)D < 30 ng/mL; n = 488].

	Score (odd ratio)
BMI	
< 25 kg/m^2	0
≥ 25 kg/m^2	1.2
Exercise	
≥3 times/week	1
1–2 times/week	1.4
lack of exercise	1.6
Sunlight exposure	
≥15 min/day	0
<15 min/day	1.7
Vitamin D dosage categories	
>20,000 IU/week	1
1–20,000 IU/week	2.3
0 IU/week	8.8
Constant	0.2
Total score	Range 4–13.6
Interpretation	<6.6 low risk ≥6.6 high risk

BMI = body mass index; ROC = Receiver Operating Characteristic.

prediction model for vitamin D deficiency in a high-risk population for osteoporosis.

In this study of Thai women who were followed for osteoporosis, the prevalence of vitamin D deficiency was high (60 %), which is consistent with previous studies in Thailand. Previous studies on Thai older men and women showed a prevalence of vitamin D deficiency (25(OH)D levels < 30 ng/mL) ranging from 34.3 % to 69.1 % [15,16]. Other studies in women with postmenopausal osteoporosis in other countries showed that this prevalence varied depending on the 25(OH)D cutoff and the study population. In one study, vitamin D deficiency, which was defined as 25(OH)D levels concentrations ≤ 20 ng/mL, was found in 28.4 % of postmenopausal women with osteoporosis [21]. However, this prevalence varied by ethnicity, with 39 % in Central Europe, 28 % in North America, 24.1 % in the Pacific Rim, and 0 % in Singapore [21]. Notably, the prevalence of vitamin D deficiency in our cohort was considerable even though 55 % received vitamin D supplementation at a median dose of 20,000 IU/week. This finding suggests the importance of lifestyles and environmental factors in determining vitamin D status [22].

Many factors affect vitamin D status, such as diet (e.g., fatty fish and fortified foods), sun exposure, ethnicity, genetic factors, obesity, drugs, and diseases that increase vitamin D metabolism [14,23]. Many studies developed prediction models for vitamin D deficiency. The most frequently reported predictors of vitamin D deficiency are age, female sex, BMI, vitamin D supplementation, fatty fish consumption, time spent outside, sun protection, suntan, exercise, smoking, alcohol, diabetes, and the season [24–31]. However, a unique model for each population group may be required because of variances in the participants' characteristics and lifestyles. In our study of women at risk for osteoporosis, age was not associated with 25(OH)D levels. In studies of women aged ≥ 50 years, some studies showed a correlation between age and vitamin D status [25,30], whereas others did not [28,29].

We conducted a comprehensive interview using a questionnaire to identify factors, such as BMI, exercise, sunlight exposure, and vitamin D supplementation, that were associated with vitamin D deficiency. A high BMI, specifically fat mass, predicted the vitamin D status [23]. The mechanisms of vitamin D deficiency are a low vitamin D intake and sun exposure in people with obesity, as well as vitamin D sequestration and volumetric dilution in a larger amount of adipose tissue [32,33]. Even though in the multivariate analysis, the OR for BMI ≥ 25 kg/m^2 is reported as 1.15, with a CI that crosses 1. Since it is well-established that BMI is a significant and clinically meaningful risk factor for vitamin D deficiency [11,12]. In addition, the model's accuracy was similar when we compared the prediction model that included BMI ≥ 25 kg/m2 with the model that did not include BMI ≥ 25 kg/m2 (area under the ROC curves were 0.747 vs. 0.740, respectively). Therefore, we kept BMI ≥ 25 kg/m2 in the final model.

A higher amount of exercise and sunlight exposure (≥15 min/day) are related to a high likelihood of having vitamin D adequacy, emphasizing the importance of sunlight in maintaining 25(OH)D levels. It should be noted that the lack of sunscreen use was only a risk factor for vitamin D deficiency in the univariate analysis, not in the multivariate analysis. We assumed it was a coincidence. Most of our participants applied sunscreen to their faces on a daily basis. Similarly, a recent study found that using sunscreen for daily photoprotection did not reduce vitamin D production from the skin [34]. In the univariate analysis, blood drawn during the summer was also associated with vitamin D deficiency. We hypothesized that sun avoidance during the summer might contribute to this finding. However, in this study, the variation in sunlight exposure across seasons was not found (data not shown). In addition, this study found an association between vitamin D and calcium supplementations. Therefore, only vitamin D supplementation was included in the multivariate models since they were clinically meaningful (higher odd ratios). However, when we included both calcium and vitamin D supplementations in the multivariate analysis, calcium supplementation did not significantly predict vitamin D deficiency (data not shown). Our study could confirm that vitamin D supplementation is more clinically meaningful than calcium supplementation in predicting vitamin D deficiency.

Our study, like other studies with a comparable demographic (women with mean aged ≥ 50 years) [25,28–30], demonstrated an association between vitamin D supplementation and 25(OH)D levels. In our cohort, participants with no vitamin D supplementation showed the highest OR for vitamin D deficiency, and the risk declined as the

Table 5
Diagnostic values of the developed risk profile for vitamin D deficiency [25(OH)D < 30 ng/mL] at different cutoffs in the total risk score (n = 488).

Cutoff in the total risk score	Percent of participants in the high-risk group	Sensitivity	Specificity	Sum of sensitivity and specificity	% Correctly	LR+	PPV	NPV
≥ 4		100	0	100	59.84	1		
≥ 6	72.3	83.6	44.4	128	67.8	1.50	69.1	64.4
≥ 6.6	57	71.9	65.3	137.2	69.3	2.07	75.5	61
≥ 6.9	50.4	66.8	74	140.8	69.7	2.56	79.3	59.9
≥ 12.5	40	54.8	82.1	136.9	65.8	3.07	82.1	54.9
≥ 13	26	37.3	90.8	128.1	58.8	4.06	85.8	49.3
≥ 13.6	10	14.7	96.9	111.6	47.8	4.81	75.2	38.6

LR = likelihood ratio; PPV = positie predictive value; NPV = negative predictive value.

supplemental dosage increased. Currently, Thailand has less vitamin D-fortified food, and Thai people are more likely to avoid the sun [35,36]. Vitamin D supplementation is a cost-effective method to correct vitamin D deficiency because of the considerable incidence of vitamin insufficiency in women at risk for osteoporosis. As a result, we reported the risk score of vitamin D deficiency while considering the dosage of vitamin D supplementation. As mentioned above, in Thailand, the only accessible prescription is for 20,000 IU of vitamin D_2. Therefore, we anticipated that our prediction model would be beneficial in this clinical context because adequate vitamin D is required for good bone health in this population during screening and treatment of osteoporosis. This model, which includes the strata of vitamin D dosage, could assist doctors to better identify people who have a high risk of vitamin D deficiency and reduce the number of 25(OH)D measurements. Measuring 25(OH)D levels is expensive and limited in availability in Thailand. This model showed acceptable discriminative capacity (area under the ROC curve: 0.747, indicating moderate discriminative ability) and goodness-of-fit. In addition, Bootstrap, a powerful technique, internally validated this predictive model. This method is useful, especially when the sample size is small. It maximizes the use of available data by repeatedly sampling from the original dataset and often using 200 to 1,000 replications from the original data [37,38]. Higher numbers of replications improve the precision of the estimator. Therefore, we use 1,000 replications for bootstrapping. This method provides a robust assessment of model performance without needing an external validation set [39].

For the clinical application, at the cut-off ≥ 6.6, the model's sensitivity, specificity, and positive predictive value were 71.9 %, 65.3 %, and 75.5 %, respectively. With this approach, a participant would have a composite score between 4 and 13.6. For example, a participant with a BMI 23 kg/m^2, exercise 1–2 times/week, sunlight exposure < 15 min/day and 20,000 IU/week of vitamin D supplementation would have a score of 5.6, indicating a low likelihood of vitamin D deficiency. A participant with a similar dose of vitamin D supplementation (20,000 IU/week) and sunlight exposure (< 15 min/day) with a BMI of 27 kg/m^2 and lack of exercise would have a score of 7, suggesting a high likelihood of vitamin D deficiency. Overall, this model correctly predicted vitamin D deficiency and excluded vitamin D deficiency for 71.9 and 65.3 %, respectively, of all participants. We propose that if this cutoff is used, 57 % of participants in this cohort would be classified as having vitamin deficiency and will need vitamin D supplementation or an increase in their current dose without measuring 25(OH)D levels. This strategy allowed us to reduce the number of 25(OH)D measurements in more than half of the participants. Despite the model having high sensitivity and low specificity, it serves a practical purpose in real-world applications. Addressing vitamin D (and calcium) deficiencies is essential for reducing fracture risk reduction in individuals with osteoporosis [40]. Although the model's low specificity may result in unnecessary supplementation for those without deficiencies, this approach is considered safe since vitamin D toxicity is rare [41]. In a prior study in Thai older adults with a hip fracture where 25(OH)D levels could not be assessed, high-dose vitamin D_2 followed by a maintenance dosage effectively restored 25(OH)D concentrations to an optimal level without causing symptomatic hypercalcemia [42]. In addition, the expense of vitamin D supplementation is significantly lower than that of 25(OH)D measurements.

To the best of our knowledge, this is the first study to investigate the predictors of vitamin D deficiency in Thai women with or at risk for osteoporosis, for whom vitamin D adequacy is required to reduce osteoporotic fracture. This result could have some clinical implications regarding reducing the number of 25(OH)D measurements. However, further randomized, controlled trials are required to confirm this strategy. A strength of our study is that 25(OH)D concentrations were measured in a single laboratory using the same method throughout the study period.

A limitation of this study is that the model cannot be generalized to different populations. Furthermore, the accuracy of 25(OH)D determination using the chemiluminescence immunoassay approach is questionable, particularly when compared with the Liquid Chromatography-Mass Spectrometer method [41]. However, we planned for this trial to be analogous to what would occur in regular practice, with blood being transferred to the central laboratory. Because a comprehensive interview conducted through the questionnaire was a component of the prediction model, recall bias could not be avoided entirely. In addition, the modified questionnaire used in this study has never been validated. If any pilot testing or validation steps were performed in Thai, it would further support the tool's reliability and relevance. This model was validated internally and would achieve better validity if external validation was performed. Finally, we did not obtain the data on Fitzpatrick skin types.

Conclusions

A questionnaire was used to identify factors associated with vitamin D deficiency in women at risk for osteoporosis at Ramathibodi Hospital, Thailand. A BMI ≥ 25 kg/m^2, insufficient exercise (no exercise or exercise 1–2 times/week), sunlight exposure < 15 min/day, and no vitamin D supplementation or vitamin D supplementation of 1–20,000 IU/week were considered in our final model. The model is considered with ROC of 0.747. At a cutoff of 6.6 in total risk score, the model predicted vitamin D deficiency with a sensitivity of 71.9 % and a specificity of 65.3 %.

Declarations

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its amendments or comparable ethical standards. Written informed consent was received from participants prior to inclusion in the study.

CRediT authorship contribution statement

Tidaporn Mullikapipat: Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data

curation. **Natee Dumrongwongsuwinai:** Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Orawin Vallibhakara:** Resources. **Sasivimol Rattanasiri:** Formal analysis. **SA Vallibhakara:** Formal analysis. **Wiwat Wajanavisit:** Resources. **Boonsong Ongphiphadhanakul:** Writing – review & editing, Conceptualization. **Hataikarn Nimitphong:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

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

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