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ORIGINAL ARTICLE

Vitamin D status and parathyroid hormone in a urban population in Vietnam

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Abstract
Summary In this cross-sectional study in Vietnam, the prevalence of vitamin D insufficiency was 46% in adult women and 20% in adult men. There was a linear inverse relationship between serum 25(OH)D and PTH concentrations, but there was no threshold of 25(OH)D at which PTH levels plateaued.
Introduction Vitamin D insufficiency is adversely associated with health outcomes. Vitamin D status in Asian populations is not well documented. This study sought to assess vitamin D status and its relationship to parathyroid hormone in a Vietnamese population.
Methods This cross-sectional study involved 205 men and 432 women aged 18–87 years, who were randomly sampled from various districts in Ho Chi Minh City (Vietnam) according to a proportional sampling scheme. Serum concentration of 25(OH)D and PTH were measured by the Electrochemiluminescence immunoassay on the Roche Elecsys 10100/201 system (Roche Diagnosis Elecsys). Vitamin D insufficiency was quantified as serum 25(OH)D levels below 30 ng/ml (75 nmol/L).
Results The average age for men and women was 43.8± 18.4 years (mean±SD) and 47.7±17.1 years, respectively. The mean 25(OH)D concentration in men (36.8±10.2 ng/mL) was significantly higher than in women (30.1±5.9; $P<$ 0.0001). The prevalence of vitamin D insufficiency in men was 20% (41/205) which was significantly lower than in women (46%, 199/432). Age, height and weight were independent predictors of 25(OH)D concentrations, and the three factors explained 15% and 5% of variance in 25(OH)D in men and women, respectively. There was a linear inverse relationship between serum 25(OH)D and PTH concentrations, but there was no threshold of 25(OH)D at which PTH levels plateaued.
Conclusions These data show that vitamin D insufficiency is common even in tropical region, and that women had a greater risk of vitamin D insufficiency than men. These data suggest that an elevation in PTH cannot be used as a marker for vitamin D deficiency.

Keywords Asian · Epidemiology · Parathyroid hormone · Prevalence · Vietnamese · Vitamin D

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Introduction

Vitamin D is a fat-soluble seco-steroid hormone which plays a key role in the regulation of bone metabolism [1]. However, in recent years there has been increasing interest in the influence of vitamin D on tissues other than bone [2, 3]. Indeed, vitamin D deficiency has been shown to be associated with increased risks of some types of cancer [4-7], type II diabetes [8-10], cardiovascular diseases [11-15], autoimmune diseases [16-18], and infectious diseases [19].

Measurement of serum 25-hydroxyvitamin D_3 is a reliable indicator of vitamin D status for an individual [20]. However, currently, there is no consensus on a cut-off level for defining vitamin D deficiency. Nevertheless, it is widely suggested that the circulating 25(OH)D levels of less than 30 ng/ml (75 nmol/L) should be considered to be vitamin D insufficient [21]. Using this definition, it has been estimated that between 40% and 100% of US and European elderly men and women living in the community are either deficient or insufficient of vitamin D [21].

Although some foods (e.g., fish, eggs, fortified milk, and cod liver oil) contain vitamin D, the main source (90% to 100%) of vitamin D is synthesis in skin from UV (sunlight) exposure [22]. As a result, it has been assumed that people living in subtropical countries are not at risk of vitamin D deficiency. Moreover, although the prevalence of vitamin D deficiency has been well documented in Caucasian populations, such a profile has not been systematically studied in subtropical Asian populations.

Vietnam is situated in the wet tropical zone, where atmospheric conditions are characterized by high temperatures and a long duration of sunshine. Vitamin D status in this population has never been studied. Thus, the present study sought to examine vitamin D status and its determinants in a Vietnamese population.

Study design and methods

Study design

The study was designed as a cross-sectional investigation in the setting of Ho Chi Minh City (formerly Saigon). The City is located at 10°45'N, 106°40'E in the southeastern region of Vietnam. The City, being close to the sea, has a tropical climate, with an average humidity of 75%. There are only two distinct seasons: the rainy season, with an average rainfall of about 1,800 mm annually (about 150 rainy days per year), usually begins in May and ends in late November; the dry season lasts from December to April. The average temperature is 28°C (82°F), the highest temperature sometimes reaches 39°C (102°F) around noon in late April, while the lowest may fall below 16°C (61°F) in the early mornings of late December. The present study had been taken place between April and October 2009.

The research protocol and procedures were approved by the Medical Ethics Committees of the People's Hospital 115 and Pham Ngoc Thach University of Medicine. All volunteer participants were provided with full information about the study's purpose and gave informed consent to participate in the study, according to the principles of medical ethics of the World Health Organization.

Study participants

Participants were randomly recruited from various districts within the Ho Chi Minh City. We approached community organizations, including church and temples, and obtained the list of members, and then randomly selected individuals aged 18 or above. We sent a letter of invitation to the selected individuals. The participants received a free health check-up, and lipid analyses, but did not receive any financial incentive. No invited participants refused to participate in the study.

Participants were excluded from the study if they had diseases deemed to affect to vitamin D metabolism such as malabsorption syndrome, or previous use of therapies that interfere with vitamin D metabolism such as rifampicin. In addition, individuals with prolonged immobility (over 2 months) were not recruited to the study.

Based on previous literature [23-28], the prevalence of vitamin D deficiency in the world populations ranged between 30% and 50%, we estimate that a sample size of 170 individuals would be adequate for estimating the prevalence within 95% confidence interval. Because we want to estimate the prevalence for each sex separately, we aimed to recruit at least 340 individuals in the study.

Data collection

A questionnaire relating to anthropometry, clinical history, lifestyle, physical activity, dietary habit, fracture, and falls, were developed and used in the data collection. The questionnaire collected anthropometric data such as age, height and weight. Age was calculated from the date of birth to the date of interview. Height without shoes (in centimeters) was measured to the nearest 0.1 cm by a wall-mounted stadiometer. Weight, without shoes or clothing, was measured (to the nearest 0.1 kg) on an electronic scale. Body mass index (BMI) was then derived as the ratio of weight (kg) over height squared (in m^2).

Each participant was asked to provide information on current and past smoking habits. This was quantified in terms of the number of pack-years consumed in each 10-year interval age group. Alcohol intake in average numbers of standard drinks per day, present as well as within the last 5 years was obtained. Sunlight exposure was assessed for mainly indoors or outdoors activities, and was quantified by the average time spent in the sun per day and per week.

Measurement of vitamin D

Fasting serum was obtained for total calcium, creatinine, liver enzymes, parathyroid hormone (PTH) and 25-hydroxyvitamin D3 [25(OH)D]. Concentration 25(OH)D and PTH in serum were measured by electrochemiluminescence immunoassay

Table 1 Characteristics of participants

Variable	Men	Women	*P* value
N	205	432	
Age, year	43.8 (18.4)	47.7 (17.1)	0.009
Weight, kg	61.1 (9.2)	52.2 (7.6)	<0.0001
Height, cm	164.2 (6.6)	153.4 (5.3)	<0.0001
Body mass index, kg/m^2	22.7 (3.2)	22.2 (3.0)	0.091
Current smoking	105 (51%)	3 (0.7%)	<0.0001
Creatinine, μmol/L	1.06 (0.16)	0.81 (0.12)	<0.0001
Serum calcium, mmol/L	2.36 (0.32)	2.37 (0.27)	0.772
PTH, ng/L	30.6 (11.2)	34.7 (14.0)	<0.0001
25(OH)D, ng/mL	36.8 (10.2)	30.1 (5.9)	<0.0001

Note: Data are shown in mean and standard deviation (in bracket)

(ECLIA) on an Roche Elecsys 10100/201 system (Roche Diagnosis Elecsys). This method can measure the concentration of 25(OH)D in the range of 4–100 ng/ml (10–250 nmol/L), and PTH in the range 1.2–500 pg/ml (0.127–530 pmol/L). The sensitivity of the assay is 1.5 ng/ml with an intraassay CV of 5.6% at 15.9 ng/ml and 11.6% at 58.9 ng/ml. The inter-assay CV at these two levels was 9 and ~12%, respectively.

Data analysis

Circulating 25(OH)D levels were classified into four groups according to the following criteria: undetectable (<15 ng/mL), deficient (<20 ng/mL), insufficient (<30 ng/mL), and sufficient (≥ 30 ng/mL) [21]. We then estimated the prevalence of vitamin D deficiency or insufficiency for each age group and sex. The association between vitamin D and anthropometric measures (age, height, and weight) was analyzed by the multiple linear regression model. The magnitude of association between risk factors and vitamin D insufficiency was measured by prevalence ratio (similar to relative risk for a prospective study) estimated by the log-binomial model [29]. Prevalence ratio rather than odds ratio was chosen, because for common outcomes (such as vitamin D insufficiency) prevalence ratio is a more appropriate measure of effect size.

In addition, we examined the functional relationship between PTH and circulating 25(OH)D by fitting a series of spline regression models to the observed data, with PTH being the dependent variable and 25(OH)D the independent variable. Each model was defined by a cut-off value of 25 (OH)D for detecting the shift in the relationship between PTH and 25(OH)D. The goodness-of-fit of the models was compared by the R-square value and Akaike Information Criterion (AIC). The model with the lowest AIC and highest R^2 value was considered the optimal model. All analyses were performed with the R package [30].

Results

The study involved 205 men and 432 women, aged between 18 and 87 years (Table 1). The average age among men was 44, which was slightly lower than that among women (48 years). Fifty-one percent of men and 0.7% of women reported being current smokers. Approximately 20% men and 13% women were obese (body mass index greater than 25 kg/m^2).

Vitamin D status

On average, men had significantly lower PTH and higher 25(OH)D concentrations than women. Using the criteria of 25(OH)D<30 ng/mL, the prevalence of vitamin D insufficiency was 20% (95% CI: 15 to 27%) in men and 46% (95% CI: 41 to 51%) in women (Fig. 1). Using the criteria of 25(OH)D<20 ng/mL, the prevalence of vitamin D deficiency was 1% (95% CI: 0.3 to 3.5%) in men and 3% (95% CI: 1.8 to 5.1%) in women. Only 2% (4/205) men

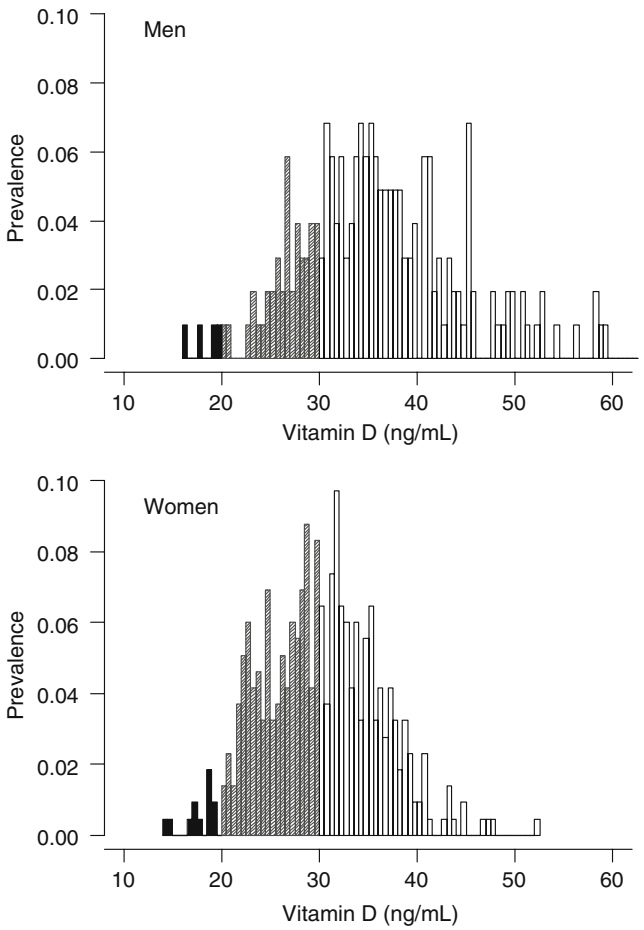

Fig. 1 Prevalence of vitamin D insufficiency in men (*upper panel*) and women (*lower panel*)

and none of the women had 25(OH)D above 60 ng/mL, the level deemed to be high (Table 2).

There was a significant difference in the prevalence of vitamin D insufficiency between age groups. In women, the prevalence was found to be highest in those aged less than 30 years (50%) and greater than 60 years (56%) compared with those aged between 30 and 60 years (40%). The same trend was also observed in men, among whom the prevalence of vitamin D insufficiency was highest in those aged less than 30 years (33%) compared with those in the age range of 30–60 (10%) and 60+ years (23%) (Fig. 2).

Predictors of vitamin D insufficiency

There was a quadratic relationship between age and 25(OH) D levels (Table 3). Moreover, in men, weight was positively correlated with 25(OH)D levels, but in women, weight was negatively correlated with 25(OH)D levels. Greater height was negatively correlated with higher levels of 25(OH)D, but the association was statistically significant in men only. The three predictors (age, weight, and height) collectively accounted for 15% and 5% of variance in 25(OH)D in men and women, respectively.

When serum 25(OH)D levels were dichotomized into two groups (insufficient vs sufficient), the risk factors for vitamin D insufficiency were age, obesity and sunlight exposure (Table 4). For example, younger men (<30 years) were more likely to have vitamin D insufficiency than those in the age range of 30–59 (prevalence ratio [PR]: 2.84; 95% CI: 1.56 to 5.18). The prevalence of vitamin D insufficiency in obese women (BMI>25) was 26% (95% CI: 2% to 56%) higher than that in non-obese women. There was no significant effect of obesity on vitamin D insufficient in men.

The median duration of sunlight exposure per week for women was 8 h (range, 1–40), which was lower than in men (median, 14 h; range, 1–56). Women who were reported sunlight exposure less than 10 h/week had a greater risk of vitamin D insufficiency than those exposed >10 h/week (PR: 1.2; 95% CI: 1.01 to 1.44). There was no significant association between self-reported duration of sunlight exposure and vitamin D status in men.

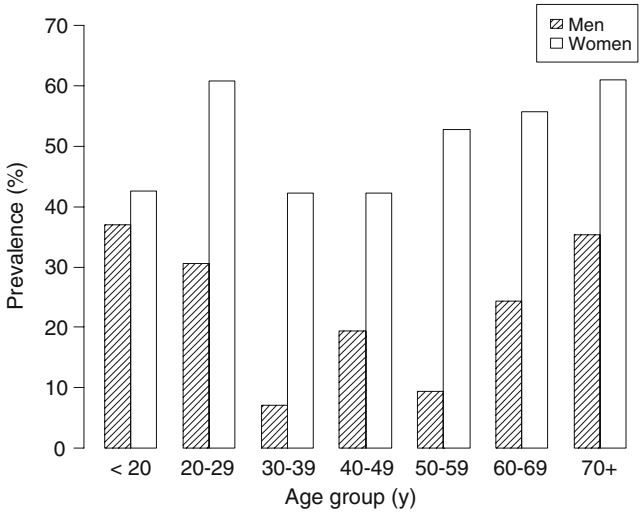

Fig. 2 Prevalence of vitamin D insufficiency [25(OH)D<30 ng/mL] by age and sex

Relationship between 25(OH)D and PTH

The relationship between 25(OH)D and PTH levels in men and women (Fig. 3) could be described by a linear regression equation as follows:

Men: PTH=34.5—0.12×VITD;
Women: PTH=42.9—0.28×VITD

The equation indicates that PTH was decreased by 0.12 ng/L in men and 0.28 ng/L in women for each 1 ng/mL increase in 25(OH)D concentration. There was no significant interaction effect between sex and 25(OH)D (P=0.11, data not shown). The two factors, 25(OH)D and sex, accounted for 3.6% of total variance in PTH. A series of spline regression models was fitted to the data with different cut-off values of 25(OH)D as "knots", but none of these spline

Table 2 Vitamin D status in men and women by various 25(OH)D cut-off values

Levels (ng/ml)	Men	Women	P value
<20	2 (1.0)	13 (3.0)	0.113
<25	10 (4.9)	82 (19.0)	<0.0001
<30	41 (20.0)	199 (46.1)	<0.0001
30–50	146 (71.2)	232 (53.7)	<0.0001
>50	18 (8.7)	1 (0.3)	<0.0001
Total	205 (100)	432 (100)	

Note: Numbers in brackets are percentage of gender-specific total.

Table 3 Predictors of 25(OH)D levels in men and women

Factors	Regression coefficients (SE) for	
	Men	Women
Age (+1 year)	0.740 (0.217)	0.34 (0.10)
Age^2 (squared)	−0.007 (0.002)	−0.0035 (0.0009)
Weight (+1 kg)	0.290 (0.085)	−0.089 (0.044)
Height (+1 cm)	−0.271 (0.137)	0.070 (0.067)
R square	0.15	0.05

Notes: Boldfaced regression coefficients indicate statistical significance at the level of P<0.05

Table 4 Risk factors for vitamin D insufficiency (25(OH)D<30 ng/mL)

Factors	Prevalence ratio and 95% CI	
	Men	Women
Age		
30–59	1.00	1.00
<30	2.84 (1.56, 5.18)	1.12 (0.88, 1.42)
>60	2.13 (1.07, 4.22)	1.25 (1.03, 1.51)
BMI>25 (yes vs no)	1.64 (0.79, 3.39)	1.26 (1.02, 1.56)
Sunlight exposure <10 h/week (yes vs no)	1.25 (0.76, 2.04)	1.21 (1.01, 1.44)

Notes: Boldfaced values indicate statistical significance at the level of $P<0.05$

models fitted better than the above simple linear regression model, suggesting that there was no cut-off value of 25(OH)D concentration at which a shift in the relationship between 25(OH)D and PTH had occurred (Fig. 4).

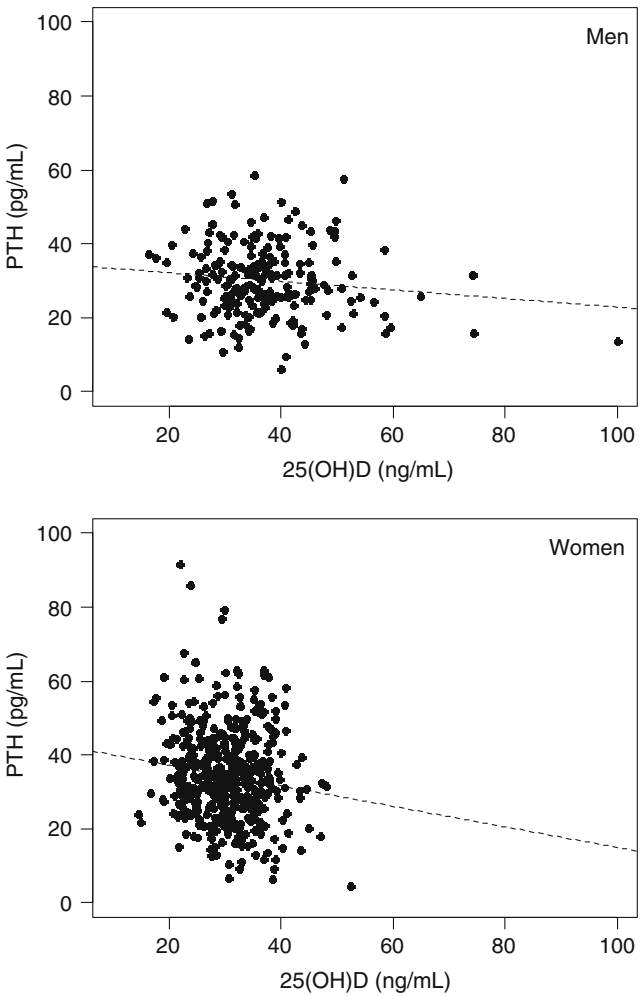

Fig. 3 Relationship between 25(OH)D and PTH levels in men (*upper panel*) and women (*lower panel*)

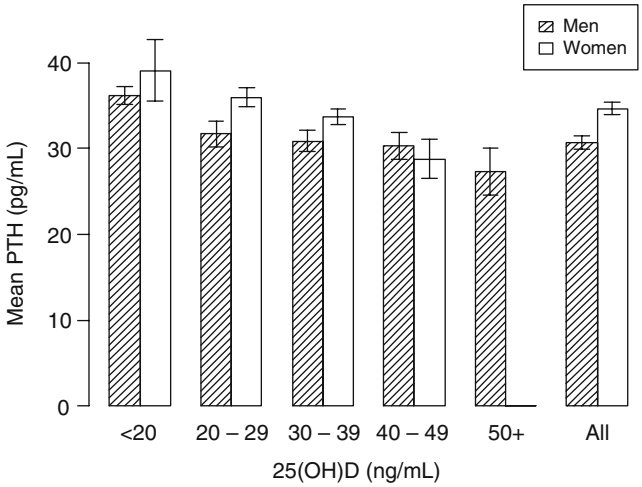

Fig. 4 Mean and standard error of PTH concentration classified by 25(OH)D concentration

Discussion

It has been assumed that Southeast Asian populations would be less likely to be prone to vitamin D insufficiency, because the region lies near the equator, with abundant of sunshine throughout the year. However, these data challenge that assumption. We have shown that 46% of adult women and 20% of adult men living in a major city of Vietnam were insufficient of vitamin D. This finding clearly suggests that vitamin D insufficiency is not only common in temperate climate countries [31], but is also highly prevalent in tropical countries [31-33]. The finding also re-affirms the observation that there is no overall correlation between latitude and vitamin D insufficiency in the world [33].

Our finding can be considered within the context of previous studies. A recent study in Hong Kong [27] reported that approximately 63% of men and women in the territory had 25(OH)D concentrations less than 30 ng/mL, a level indicative of vitamin D insufficiency. In an analysis of 240 anonymized blood samples from healthy ambulatory outpatients in Singapore, the prevalence of vitamin D insufficiency (25(OH)D<30 ng/mL) ranged from 85% in Chinese women and 90% in Malaysian men to 100% in Malaysian and Indian women [25]. The prevalence of vitamin D insufficiency in these populations is in fact highly comparable to that observed in the Japanese population, among whom, 82% postmenopausal women had 25(OH)D levels below 30 ng/mL [34]. Our study's finding, taken together with previous studies [31-33], confirm the view that vitamin D insufficiency is endemic in the world, and that equatorial climates are not protective.

In this study, men had higher levels of vitamin D than women, such that the prevalence of vitamin D insufficiency in men was only half of that in women, consistent with data

from Singapore [25]. However, this finding is not consistent with data from Hong Kong [27] where men had a greater risk of vitamin D insufficiency than women. Personal factors such as clothing and dressing styles may be the sources of the sex differences. Asian women, including Vietnamese women, tend to have a negative attitude toward sunlight and take measures (such as wearing face masks when riding motorbikes) to avoid sunlight exposure [35]. This attitude and differences in clothing coverage of skin probably explain the prevalence of vitamin D insufficiency being higher in Vietnamese women than in men.

The prevalence of vitamin D insufficiency varied significantly by age groups. Individuals aged <30 years and more >60 years were 1.2 and 1.3 time more likely to be vitamin D insufficient than those between those ages. As a cultural norm, young Vietnamese men and women perceive white skin as a mark of attractiveness and a measure of high social class, and as a result, they seek to avoid being exposed to sunlight. Indeed, a large proportion of young women (~54%) and men (36%) in this study reported that they were exposed to sunlight less than 10 h a week, and this could explain the disparity in the prevalence of vitamin D insufficiency among age groups.

In this study, we found that age, weight, and height were the main predictors of serum 25(OH)D concentrations; however, the relationships differed between sexes. While greater weight was associated with lower 25(OH)D concentrations in women, the opposite association, albeit insignificant, was noted in men. Greater body mass index has been associated with lower 25(OH)D levels in previous studies [36-38], such that those with BMI >40 kg/m^2 had 24% lower serum 25(OH)D levels than those with BMI <25 kg/m^2 [36], probably due to the reduction in bioavailability of vitamin D3 from cutaneous fat mass [39].

At present, there is no consensus on the threshold of 25 (OH)D to define "vitamin D deficiency." Such a threshold may be determined based on the relationships between OH [25]D and PTH, calcium absorption, bone loss, fracture risk, and fall. Based on the relationship between vitamin D and calcium absorption and fracture, it has been proposed that a serum 25(OH)D levels of 32 ng/mL or higher is sufficient [40]. In an analysis using data from a French sample, serum PTH did not change when 25(OH)D concentrations were above 31 ng/mL, but when 25(OH)D concentrations fell below this threshold, PTH increased [41]. The present study found that although there was an inverse association between PTH and 25(OH)D levels (which is consistent with previous studies [28, 42, 43]), there was no thresholds for 25(OH)D at which PTH levels plateaued. Indeed, the relationship between PTH and 25 (OH)D was linear, such that PTH progressively decreased as 25(OH)D levels increased. The modest linear correlation (r=−0.17) between PTH and 25(OH)D levels seems to suggest that it is not appropriate to use elevated serum levels of PTH as a surrogate marker for 25(OH)D insufficiency. This is probably true as PTH is modulated by several other factors, particularly calcium intake. In this study, we did not assess dietary calcium intakes, but typical Vietnamese diets in general contain little dairy and thus have low calcium [44].

The present study represents one of the largest studies of vitamin D status in Asian populations. As such, it increased the reliability of estimates of vitamin D insufficiency in age-and-sex subgroups that is otherwise not possible in studies with small sample sizes. The study population is highly homogeneous, which reduces the effects of potential ethnic confounders that could compromise the estimates. Moreover, the technique of measurement of 25(OH)D was a novel Elecsys Vitamin D3 automated assay, which has been shown to be a precise method for measuring 25(OH)D over a wide reportable range in serum. Indeed, recent studies have shown that measurement of 25(OH)D by this method was highly concordant with the HPLC and liquid chromatography tandem mass spectrometry methods [45]. Nevertheless, the study has a number of potential weaknesses. 25-hydroxyvitamin D2 (ergocalciferol) was not measured in this study; however, the occurrence of this vitamin D (less than 10% of sera) seems not to be a major problem. Because the study was a cross-sectional investigation, no causal inferences could be made for the observed relationships between factors. As is the case of all observational studies, healthy individuals were more likely to participate in the study, and this could have introduced selection bias into the study. The participants in this study were sampled from an urban population; as a result, the study's finding may not be generalizable to the rural population.

Vitamin D plays an important role in maintaining health [40, 46-49]. Besides the main role of regulating calcium and PTH, vitamin D also exerts its effects on the neuromuscular system, insulin level, cancer and immunity [3]. Indeed, vitamin D effects on many chronic diseases such as osteoporosis, type 2 diabetes, cancer and cardiovascular diseases [50]. In a recent meta-analysis, there was an association between vitamin D deficiency and mortality [51], and supplementation with 300–2,000UI of vitamin D was associated with a reduction in mortality risk [52]. Therefore, the finding that approximately half of women and a-fifth of men in this population were vitamin D insufficient implies that a large population is at risk of detrimental bone health (e.g., increased fracture risk), chronic diseases, and even increased risk of mortality.

In conclusion, these data showed that 46% of adult women and 20% of adult men in a urban population in Vietnam had vitamin D insufficiency. This finding points to the need for assessment of vitamin D status in the general

population, as living in an abundant sunshine region does not protect against vitamin D insufficiency. These results also suggest a need to review recommendations for vitamin D nutrition and for determining optimal levels of vitamin D in Asian populations.

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Conflicts of interest All authors declare that they have no conflict of interest with regard to this study. Professor Tuan Nguyen received honorarium for speaking and providing consultant services to MSD Vietnam Ltd, Sanofi-Aventis, Novartis, and Roche. Professor John Eisman serves as a consultant and receives corporate appointment from Amgen, deCode, Eli Lilly and Company, GE-Lunar, Merck Sharp & Dohme Ltd., Novartis, Organon, Roche-GSK, sanofi-aventis and Servier.

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