Chapter 5

Is Serum 25-hydroxyvitamin D Associated with Health among Chinese in the Netherlands? A Cross-sectional Study

Ping Wai Man[1], Irene M. van der Meer[2], Wenzhi Lin[3], Ron Wolterbeek[4], Mattijs E. Numans[1], Annemieke C. Heijboer[5,6], Paul Lips[7], Barend J.C. Middelkoop[1,2]

[1]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

[2]Department of Epidemiology, Municipal Health Service Haaglanden, The Hague, The Netherlands

[3]Medical Center Balans, The Hague, The Netherlands

[4]Medical Statistics, Department of Biomedical Data Science, Leiden University Medical Center, Leiden, The Netherlands

[5]Department of Clinical Chemistry, Endocrine Laboratory, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands

[6]Laboratory of Endocrinology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[7]Department of Internal Medicine, Endocrine Section, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands

Journal of Clinical Nutrition and Food Science 2019;2(3):079-086

ABSTRACT

Background: Little is known about the association between 25-hydroxyvitamin D [25(OH)D] and health outcomes of Chinese people residing in the Netherlands.

Objective: The purpose of our cross-sectional study was to explore the associations between 25(OH)D and bone health, cardio metabolic-related outcomes, and physical performance.

Methods: In a sample of Chinese people living in the Netherlands, 416 men and women aged ≥18 years with a Chinese background, serum 25(OH)D concentrations, fasting blood glucose, total cholesterol, systolic and diastolic blood pressure, body mass index, waist circumference, and physical performance were measured. Bone health was measured by means of quantitative ultrasound of the heel. Physical activity, sunlight exposure, calcium intake, and use of vitamin D supplements and drugs were self-reported by means of questionnaires.

Results: At the cut-off point of 25(OH)D for vitamin D adequacy as defined by the Health Council of the Netherlands (HCN), fasting blood glucose was higher when serum 25(OH)D was <30 nmol/L (or <50 nmol/L for persons aged ≥70 years) both unadjusted (0.340 mmol/L; 95% CI, 0.059 to 0.621) and adjusted for age, sex and use of vitamin D supplements and glucose-lowering drugs (0.284 mmol/L; 95% CI, 0.033 to 0.536). Other associations at the HCN cut-off point were not found. At the cut-off points of 25(OH)D of 50 nmol/L and 75 nmol/L no associations between 25(OH)D and health outcomes were found.

Conclusion: Although this study provides some insights into detectable associations between vitamin D and some health outcomes, further longitudinal and intervention studies are required to confirm our findings.

Keywords: Cardio metabolic, Chinese, Fasting blood glucose, 25-Hydroxyvitamin D, Health outcomes

INTRODUCTION

Vitamin D_3 is produced by the epidermis when 7-dehydrocholesterol is converted to vitamin D_3 under exposure to ultraviolet B radiation. It can also be obtained by some dietary means (e.g. fatty fish) and from food fortified with vitamin D_3 (e.g. margarine and cooking oils). Vitamin D_2 originates from irradiation of the plant sterol ergosterol. Although still available in some (multi) vitamin products, it has been more and more replaced by vitamin D_3. The metabolism of vitamin D_2 is similar to that of vitamin D_3 [1].

Vitamin D is converted in the liver into 25-hydroxyvitamin D [25(OH)D] which is not biologically active but used as an indicator of total body vitamin D status. Subsequently, 25(OH)D is hydroxylated in the kidneys into its biologically active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] [2, 3].

The benefits of an adequate vitamin D status on bone health are well known. It regulates calcium metabolism and homeostasis, and facilitates intestinal absorption of calcium and phosphorus for mineralization of the skeleton. A positive association has been found between serum 25(OH)D concentration and bone mineral density (BMD) [1, 4, 5]. Low serum 25(OH)D concentration and low BMD are predictors of osteoporotic fractures [6, 7], whereas a sufficient vitamin D status may protect older adults (especially less active women) from falling [8, 9]. Lower 25(OH)D concentrations have also been associated with a higher risk of non-skeletal diseases, e.g. cancer, diabetes, metabolic syndrome, and cardiovascular, infectious and autoimmune diseases [10-14]. By contrast, an umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials found no clear role of vitamin D for any outcome, including skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases, although some associations were considered probable [15]. Recently, a large, ethnic divers randomized placebo controlled trial did not find a lower incidence of invasive cancer or cardiovascular events than placebo after vitamin D supplementation of 2000 IU/day and omega-3 fatty acids (1 g/day) [16].

Relationships between 25(OH)D and health outcomes may be dependent on 25(OH)D thresholds [17-19]; however, the cut-off value for optimal 25(OH)D concentration is still being debated and different thresholds may exist for different outcomes. Thresholds may be based on serum 25(OH)D concentrations at which parathyroid hormone (PTH) levels are maximally suppressed [1], or on 25(OH)D levels at which a further increase is not associated with an increase in BMD [4, 5]. The Health Council of the Netherlands (HCN) has set the required 25(OH)D level at 30 nmol/L for persons aged 0-70 years and at 50 nmol/L for persons aged ≥70 years, based on reducing the risk of rickets in children and of bone fractures in older persons [20]. The US Institute of Medicine recommends a 25(OH)D level of ≥50 nmol/L

for all ages in relation to bone health [21], while the Endocrine Society advocates 25(OH)D levels of ≥75 nmol/L for all ages to maximize the health effects of vitamin D [22].

It has been suggested that thresholds of 25(OH)D as used in white populations may not apply to other populations [23, 24]. Furthermore, relationships between 25(OH)D and health outcomes may also differ by race and ethnicity [23, 25, 26]. Finally, vitamin D status and associations between vitamin D and health of Chinese populations globally may not be uniform [27].

In the present cross-sectional study we aimed to explore, in a sample of Chinese people living in the Netherlands, the associations between 25(OH)D and heel bone health, cardio metabolic-related outcomes, and physical performance.

MATERIALS AND METHODS

Study population

This cross-sectional investigation was part of an observational study on vitamin D status in a Chinese population in the Netherlands [28]. Briefly, men and women aged 18 years and older with a Chinese background and living in the Netherlands were eligible to participate when they, or at least one parent, were born in mainland China, Hong Kong or Taiwan. Participants were recruited through Chinese welfare, elderly, and women organizations from four cities in the Netherlands with the largest Chinese communities (The Hague, Amsterdam, Rotterdam, and Utrecht) and also through social media. All participants, also those who suffered from diseases, e.g. diabetes, hyperlipidemia or hypertension, were included in the analyses.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Medical Ethical Committee of the Leiden University Medical Center (approval number P13.279). Written informed consent was obtained from all participants.

Measurements of serum 25(OH)D concentrations

Serum 25(OH)D concentrations were measured by isotope dilution/online solid-phase extraction liquid chromatography-tandem mass spectrometry (ID-XLC-MS/MS), and performed at the Endocrine Laboratory of the Amsterdam UMC, Vrije Universiteit Amsterdam in March 2014 [29]. In short, deuterated internal standard [25(OH)D-d6] was added to the samples and 25(OH)D was released from its binding proteins with acetonitrile. Samples were extracted and analyzed by XLC-MS/MS [a Symbiosis online SPE system (Spark Holland,

Emmen, the Netherlands)] coupled to a Quattro Premier XE tandem mass spectrometer (Waters Corp., Milford, MA, USA). The limit of quantitation (LOQ) was 4.0 nmol/L, intraassay CV was <6%, and interassay CV was <8% for concentrations of 25-180 nmol/L.

Measurement of heel bone

Heel bone was measured by quantitative ultrasound (QUS) (Sahara Clinical Bone Sonometer, Hologic, Bedford, MA, USA) which, compared to dual-energy X-ray absorptiometry (DXA) is a less expensive, transportable, and non-ionizing scanner. It determines three ultrasound parameters from the measured signal: speed of sound (SOS, in m/s), broadband ultrasound attenuation (BUA, in dB/MHz), and the quantitative ultrasound index (QUI). The QUI is a composite parameter which combines SOS and BUA to simplify the interpretation of QUS results. QUI values normally range from 0-150, with higher values obtained for young healthy persons, and lower values obtained for older or osteoporotic persons. Daily calibration was performed before measurement according to the manufacturer's recommendations.

Measurements of fasting blood glucose and total cholesterol

Blood was drawn after overnight fasting for the measurement of 25(OH)D, fasting blood glucose (FBG), and total cholesterol (TC). All blood measurements were performed at the Endocrine Laboratory of the Vrije Universiteit Amsterdam in March 2014.

Plasma glucose was collected in tubes containing NaF as an anti-glycolysis component and measured using an enzymatic ultraviolet reference method (Roche). The repeatability (n=21) was 0.6%, CV (EP15) was 1.2%, and the lower and upper LOQ was 0.11-41.6 mmol/L.

Cholesterol was measured by a colorimetric enzymatic method (Roche). The repeatability was 0.9%, CV (EP15) was 1.5%, and the lower and upper LOQ was 0.1-20.7 mmol/L.

Determination of blood pressure, body mass index, waist circumference, and physical performance

Blood pressure was measured in a sitting position after at least 10 min of rest by a Microlife WatchBP Office device (Microlife AG, Wildnau, Switzerland), which automatically takes three consecutive measurements at 1 min intervals by default. The result of these three measurements was automatically averaged to produce values of systolic (SBP) and diastolic blood pressure (DBP).

Height (cm) and weight (kg) were measured in standing position and wearing light clothing and no shoes. The body mass index (BMI, kg/m^2) was calculated as body weight divided by squared body height.

Waist circumference (WC) was measured with a flexible tape all around the body at the level of the navel over thin clothing.

To examine physical performances, participants were asked to perform short physical tests, as previously described [30]. In short, these included the time taken to walk 3 m, turn 180° and walk back (walking test); time taken to rise five times from a kitchen chair with arms folded in front of the chest (chair stands); and the ability to stand with the heel of one foot directly in front of, and touching the toes of the other foot for at least 10 s (tandem stand). A highest score of four points was given to the fastest quartile to accomplish walking and chair tests and for the ability to hold position for at least 10 s in the tandem test, resulting in a maximum individual physical performance score (PPS) of 12 points [30].

Physical activity was self-reported and defined as moderate strenuous effort for at least 30 min, e.g. walking, cycling, or gardening.

Statistical analysis

To examine the characteristics of the participants according to four categories of 25(OH)D (<30, 30-49.9, 50-74.9 and ≥75 nmol/L), the means of normally distributed continuous variables were compared by One-way ANOVA and those of categorical variables using the Chi-square test (Table 1).

Because of the current lack of consensus regarding threshold levels, cut-off points of 25(OH)D were used as recommended by the HCN and the Endocrine Society, and the suggested serum 25(OH)D level of the US Institute of Medicine of at least 50 nmol/L at which almost all persons are vitamin D-sufficient.

Therefore, 25(OH)D concentration was dichotomized into lower or higher than 50 and 75 nmol/L, and also according to the criteria of the HCN (yes/no), i.e. participants were considered to be vitamin D-sufficient when serum 25(OH)D concentration was at least 30 nmol/L when aged 0-70 years, and at least 50 nmol/L when aged 70 years and over. Using these three cut-off points of 25(OH)D (independent variables), and the continuous outcomes QUI, FBG, TC, SBP, DBP, BMI, WC, and PPS (dependent variables), multiple linear regression analysis was performed. Age and sex were continuously maintained in the model for biological relevance. Use of vitamin D supplements and of glucose-, cholesterol-, and blood pressure-lowering drugs were added in the model as covariates and also examined as effect modifiers by testing whether interaction terms were statistically significant, to explore possible differential effects between users and non-users of vitamin D supplements or drugs. In addition, we examined the possible effect modification of the use of dairy products by adding the product term of 25(OH)D * dairy use to the model. Interaction terms were main-

tained in the model when statistically significant. Considering the exploratory nature of our study, we chose not to correct for multiple comparisons.

Table 1. Characteristics of the participants according to their level of 25(OH)D

	25(OH)D (nmol/L)				
	<30	30-49.9	50-74.9	≥75	p
Number of participants (%)	77 (18.5)	159 (38.2)	96 (23.1)	84 (20.2)	
Men (%)	18 (23.4)	52 (32.7)	20 (20.8)	13 (15.5)	0.017
Age (years)	53.6 (13.4)	55.3 (12.6)	56.0 (10.8)	61.0 (10.2)	<0.001
QUI	99.0 (20.1)	97.4 (19.1)	99.0 (17.5)	96.0 (17.8)	0.647
FBG (mmol/L)	5.7 (1.7)	5.6 (1.2)	5.7 (1.0)	5.6 (0.9)	0.739
TC (mmol/L)	5.4 (1.1)	5.4 (1.0)	5.4 (1.0)	5.5 (1.1)	0.888
SBP (mmHg)	132 (22)	134 (20)	136 (21)	136 (20)	0.574
DBP (mmHg)	79 (10)	80 (11)	80 (12)	78 (9)	0.212
BMI (kg/m^2)	24.2 (3.4)	24.3 (3.1)	24.7 (3.7)	23.9 (4.0)	0.565
WC (cm)	84.9 (9.9)	85.7 (10.4)	85.9 (9.5)	86.1 (11.5)	0.691
Current smoker (%)	2 (2.7)	9 (5.8)	3 (3.3)	2 (2.4)	0.501
Users of					
vitamin D supplements (%)	6 (7.9)	25 (15.8)	37 (38.5)	60 (73.2)	<0.001
glucose-lowering drugs (%)	4 (5.3)	7 (4.5)	9 (9.6)	10 (12.0)	0.121
cholesterol-lowering drugs (%)	11 (14.5)	17 (10.9)	19 (20.4)	19 (22.9)	0.061
blood pressure-lowering drugs (%)	9 (12.2)	26 (16.6)	27 (28.7)	20 (24.4)	0.024
PPS	8.95 (2.22)	9.09 (2.20)	8.99 (2.31)	8.98 (2.41)	0.961
Consumption of dairy products (n=406) (%)					
no use of dairy products	31 (41.9)	62 (39.7)	36 (37.5)	21 (26.3)	0.157
1-2 servings/day	43 (58.1)	93 (59.6)	57 (59.4)	58 (72.5)	
≥3 servings/day	0	1 (0.6)	3 (3.1)	1 (1.3)	
Sunlight exposure (n=407) (%)					
never	17 (22.4)	25 (15.7)	11 (11.5)	12 (14.5)	0.266
occasionally/often	52 (77.6)	134 (84.3)	85 (88.5)	71 (85.5)	
Physical activity ≥3 days/week (%)	28 (36.8)	52 (32.7)	44 (46.8)	42 (50.0)	0.028

Data are expressed as numbers (%), means (SD) unless otherwise indicated.
QUI, quantitative ultrasound index; FBG, fasting blood glucose; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; PPS, physical performance score. One serving of dairy product is defined as a glass of milk, buttermilk, yogurt, or a slice of cheese.

Results are expressed as regression coefficient B, 95% confidence interval (CI), or p-value. A p-value <0.05 was considered to be statistically significant.

Analyses were performed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp. Armonk, NY, USA).

RESULTS

Of the 416 participants [mean age (SD) 56.3 (12.1) years], 103 (24.8%) were men. Men had a significantly lower median serum 25(OH)D concentration than women (42.0 nmol/L vs 47.0 nmol/L, respectively, p = 0.046), higher mean BMI [25.4 (3.6) vs 23.9 (3.4) kg/m^2, respectively, p <0.001] and higher mean WC [89.9 (11.0) vs 84.1 (9.7) cm, respectively, p <0.001] (data not shown). Previously, we have reported that 18.4% of men and 35.5% of women used vitamin D supplements. The estimated average quantity was 500 IU and 650 IU per day, respectively [28].

Participants in the ≥75 nmol/L category of serum 25(OH)D were significantly older than participants in lower categories of 25(OH)D, and also the number of users of vitamin D supplements was higher.

Participants in the category 50-74.9 nmol/L used significantly more blood pressure-lowering drugs than those in the lowest category of serum 25(OH)D (<30 nmol/L). Physical activity (≥3 days per week moderate strenuous effort for at least 30 min) was significantly more reported among participants in the highest serum 25(OH)D category (≥75 nmol/L) than in the 25(OH)D category 30-49.9 nmol/L. Across the categories, no significant difference was found in the number of users of glucose-lowering and cholesterol-lowering drugs (Table 1).

The results of the multiple linear regression analyses are shown in Table 2. Fasting blood glucose was significantly higher in participants with serum 25(OH)D concentrations <30 nmol/L (or <50 nmol/L for persons ≥70 years), both unadjusted (0.340 mmol/L; 95% CI, 0.059 to 0.621) and adjusted for age, sex and use of vitamin D supplements and glucose-lowering drugs (0.284 mmol/L; 95% CI, 0.033 to 0.536). No association was found between serum 25(OH)D concentrations and other cardio metabolic-related outcomes, QUI or physical performance. Further adjustment for physical activity in all models had no appreciable effect on the results (data not shown).

Interaction terms of serum 25(OH)D with use of vitamin D supplements or with drugs were not significant, except for SBP at the cut-off point of 75 nmol/L, where the change was in an opposite direction for users and non-users of antihypertensive drugs (p = 0.038) and, moreover, the two associations separately showed no significant difference. Participants with a serum 25(OH)D concentration <75 nmol/L and not using blood pressure-lowering drugs had higher SBP than participants with serum 25(OH)D concentration ≥75 nmol/L (3.77 mmHg, p = 0.181), whereas participants with serum 25(OH)D concentration <75 nmol/L who did use antihypertensive drugs had lower SBP compared to those with serum 25(OH)D concentration ≥75 nmol/L (-7.54 mmHg, p = 0.131). The interaction term of 25(OH)D with the use of dairy products in all models was not significant (data not shown).

Table 2. Associations between cut-off points of 25(OH)D (nmol/L) and health outcomes, adjusted for age, sex, use of vitamin D supplements, and use of relevant medication [a, b, c]

		25(OH)D (nmol/L)		
		n-HCN vs HCN	<50 vs ≥50	<75 vs ≥75
	N	B (95% CI)	B (95% CI)	B (95% CI)
QUI	413	-0.089 (-4.279 to 4.101)	-1.497 (-5.322 to 2.329)	-0.535 (-5.348 to 4.278)
FBG (mmol/L) [a]	400	0.284 (0.033 to 0.536)	0.058 (-0.178 to 0.293)	0.142 (-0.152 to 0.435)
TC (mmol/L) [b]	401	-0.120 (-0.345 to 0.105)	-0.082 (-0.292 to 0.128)	-0.075 (-0.335 to 0.185)
SBP (mmHg) [c]	404	0.823 (-3.644 to 5.289)	0.240 (-3.845 to 4.325)	0.142 (-0.152 to 0.435)
DBP (mmHg) [c]	404	-0.821 (-3.324 to 1.681)	0.184 (-2.106 to 2.475)	1.844 (-0.995 to 4.683)
BMI (kg/m^2)	413	-0.098 (-0.920 to 0.725)	-0.247 (-0.998 to 0.505)	0.443 (-0.501 to 1.387)
WC (cm)	413	0.247 (-2.053 to 2.546)	-0.204 (-2.305 to 1.897)	0.637 (-2.004 to 3.277)
PPS	411	-0.264 (-0.771 to 0.244)	-0.103 (-0.567 to 0.361)	-0.279 (-0.865 to 0.306)

(n-)HCN, (not) according to the criteria of the Health Council of the Netherlands [i.e. serum 25(OH)D (not) ≥30 nmol/L (for persons <70 y) or (not) ≥50 nmol/L (for persons ≥70y)]; QUI, quantitative ultrasound index; FBG, fasting blood glucose; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; PPS, physical performance score.

[a] adjusted for use of glucose-lowering drugs, [b] adjusted for use of cholesterol-lowering drugs, [c] adjusted for use of blood pressure-lowering drugs

DISCUSSION

The present cross-sectional study explored the associations between serum 25(OH)D and bone health, and cardio metabolic-related health outcomes, and physical performance, in a sample of Chinese people residing in the Netherlands. Findings from our study showed that FBG was significantly higher when serum 25(OH)D was <30 nmol/L (or <50 nmol/L for persons ≥70 years).

Previous studies have shown that low serum 25(OH)D concentrations are associated with higher fasting glucose levels and decreased insulin release, possibly through reduced stimulation of the vitamin D receptor in the pancreatic β-cell [31, 32]. In two Chinese studies, with mean serum 25(OH)D concentrations of 40 and 67 nmol/L, serum 25(OH)D was inversely associated with FBG [33, 34]. By contrast, no significantly lower risk of diabetes than placebo was found after vitamin D supplementation (4000 IU/day) in a study among high risk type 2 diabetes persons [35]. In a multi-ethnic study performed in the Netherlands among Western, Turkish, Moroccan, Surinamese South Asian, Surinamese Creole and sub-Saharan African people, lower vitamin D levels were associated with a higher prevalence of diabetes. However, this association was not significant anymore after adjustment for age, sex, BMI, season, and ethnic group [36]. Although we found that FBG was associated with lower serum 25(OH)D concentrations, further research is, however, needed to determine

whether vitamin D indeed plays an important role in glycemic status in our study population.

A multi-ethnic study observed among Chinese participants a borderline statistical significance of lower serum 25(OH)D concentrations with lower BMD levels, measured with DXA, after adjustment for osteoporosis risk factors [26]. By contrast, a randomized clinical trial performed in Canada among 311 healthy adults, found no benefit of high dose vitamin D supplementation (4000 IU/day or 10 000 IU/day compared with 400 IU/day) for bone health [37]. For practical reasons, we measured bone health by means of QUS of the heel. The QUS parameter, the QUI, is associated with BMD and probably predicts fracture risk as well as DXA [38]. Studies on associations between serum 25(OH)D and QUS have shown conflicting results, which may be due to differences in the assay methods used for measurement of 25(OH)D or the site of bone measurement, and/or to adjustments made for confounders and effect modifiers [39-41]. In the present study no association was found between serum 25(OH)D and QUI; a possible explanation for this might be that heel bone parameters were positively influenced by mechanical loading through standing (e.g. at work) as it is plausible to assume that at least a substantial part of our study population work in the restaurant business. Furthermore, the level of calcium may also have influenced bone parameters. For example, low calcium intake may lead to secondary hyperparathyroidism, resulting in bone loss [1]. Studies conducted in mainland China and Hong Kong showed that the Chinese diet contains <500 mg calcium per day [42, 43]. However, intestinal calcium absorption was more than two-fold higher than that reported in white and black populations [43]. Moreover, Chinese children and adolescents, and also black children, have been found to have higher fractional calcium absorption than Caucasian children [44, 45]. From the data in our study, total calcium intake cannot be determined exactly. However, almost 60% of our participants used daily dairy products and almost 15% used calcium supplements. Previously, we estimated that in the present study population, the calcium intake by dairy products was 240 mg per day [28]. Also taking into account the above mentioned good intestinal calcium absorption among Chinese, we suppose that the average daily calcium intake may have been sufficient in our study population. Moreover, associations between serum 25(OH)D and health outcomes did not change by adding the interaction term of serum 25(OH)D with use of dairy products to the models.

In the present study, no association was found between serum 25(OH)D and TC. Previous studies on associations between 25(OH)D and TC are conflicting. For example, one Chinese study found that vitamin D deficiency (serum 25(OH)D <50 nmol/L) was associated with an increase in TC levels [46], whereas another Chinese study observed a positive association between serum 25(OH)D and TC in men and women after adjustment for age and BMI [47].

We did not observe an association of serum 25(OH)D with SBP, although below compared to above the serum 25(OH)D cut-off point of 75 nmol/L the change was in an opposite direction for users and non-users of antihypertensive drugs, resulting in a significant effect modification. Also, no association was found between serum 25(OH)D and DBP. Inconsistent results were found in previous Chinese studies regarding this relationship. Whereas one study found that DBP, but not SBP, was inversely associated with serum 25(OH)D [33], another study showed no association between serum 25(OH)D and blood pressure [34]. In the Dutch LASA study, low serum 25(OH)D was associated with a higher risk of hypertension [18]. However, a recent systematic review and meta-analysis concluded that vitamin D supplementation might not have an effect on SBP or DBP, in either hypertensive or normotensive persons [48].

Serum 25(OH)D levels are known to be lower in obese people and inversely associated with BMI [49]; this is likely caused by a greater distribution volume of lipid soluble vitamin D, or because of less sun exposure [50]. Most studies examining the relationship between vitamin D status and BMI were performed among obese Caucasian individuals (BMI ≥30 kg/m^2) [51, 52]. We observed no association between serum 25(OH)D and BMI, possibly due to a restriction in the range of observed values of the BMI. Similarly, we found no association between vitamin D status and WC (an indicator of abdominal fat accumulation).

Also, no association was found between serum 25(OH)D and physical performance score or any of its components. Theoretically, physical performance scores ranged from 0-12 points (our scores at the 25th, 50th, and 75th percentile were 7, 9, and 11 points, respectively). This lack of a large variation in scores could have limited the possibility of finding an association between serum 25(OH)D and physical performance score. This may indicate that our adult study population was not sufficiently vulnerable to detect an association between serum 25(OH)D and physical performance, as our participants consisted of relatively young and ambulatory Chinese individuals. Also, our study population was possibly less dependent on vitamin D due to other health protective factors (e.g. physical activity). However, adjustment for physical activity had no effect on the results (data not shown). In the aforementioned multi-ethnic study performed in the Netherlands, also no unambiguous association between serum 25(OH)D concentration and muscle-related outcomes was found [36].

Strength of the present study is that all measurements were performed in March 2014 (implying virtually no influence of sun exposure), blood was drawn after overnight fasting, and our participants had a relatively representative age distribution. Furthermore, serum 25(OH)D concentration was measured using the gold-standard LC-MS/MS method. The study also has several limitations. First, because of our cross-sectional study design, we have no prospective data on serum 25(OH)D concentrations and the examined health outcomes,

and therefore, causal relationships cannot be assessed. For example, chronic patients may have started vitamin D supplement use on their doctor's advice, thus masking the deleterious effect of low vitamin D status that may have existed before. We cannot rule out this possibility completely, among others, because we do not know the start date of possible supplement use. If frequent consultations, as a chronic disease such as diabetes usually requires, would have been responsible for a substantial increase in supplement use, usage of vitamin D supplements should be more frequent in diabetes patients. However, additional analyses showed this not to be the case (data not shown). Second, we also did not measure individual components of TC, e.g. HDL or LDL concentrations, or triglycerides and we did not precisely register the use of possibly anti-osteoporotic medication of the participants. Third, physical activity, sunlight exposure, calcium intake, and use of vitamin D supplements and drugs were self-reported which carries the risk of response bias. Fourth, women were overrepresented, possibly because Chinese women in the Netherlands are more health-conscious than Chinese men and, therefore, more willing to participate in health projects. Furthermore, other unobserved confounders may have biased the results. Finally, our findings are not generalizable to Chinese populations outside the Netherlands as vitamin D status may not be uniform for Chinese populations living elsewhere. Differences in personal behavior (especially women for cosmetic reasons), clothing habits, availability of vitamin D rich food (e.g. fatty fish and sun-dried mushrooms), use of vitamin D supplements, latitude of the area, and indoor and outdoor occupational and recreational activities are reasons why vitamin D status may differ among Chinese populations [27].

In conclusion, in this cross-sectional study, FBG seems to be higher in case of low serum 25(OH)D concentration. Associations between serum 25(OH)D and other cardio metabolic-related health outcome, QUI or physical performance were not found. Before any recommendations regarding vitamin D can be made in this population, further longitudinal and intervention studies are, however, needed to confirm our results.

Acknowledgments

The authors thank all responders for their participation and all volunteers for their efforts.

Financial support

The authors gratefully acknowledge financial support from 'Stichting Artrose Zorg' (grant number Staz20140117), and 'Fonds voor het Hart' (grant number FVH20140311). The funders had no role in the design, analysis or writing of this article.

Conflict of interest

Paul Lips has received a lecture fee from Abiogen. The other authors declare that they have no conflict of interest.

Authorship

PWM was involved in the study design, participated in the data collection, was involved in the analysis and interpretation of the data, and drafted the first version of the manuscript. IvdM was involved in the study design, the analysis and interpretation of the data, and participated in writing the manuscript. WL was involved in the study design and participated in the data collection. RW was involved in the analysis and interpretation of the data. MEN contributed to the study design. ACH was involved in the data collection. PL and BJCM were involved in the study design, and the analysis and interpretation of the data. All authors revised the manuscript for important intellectual content.

REFERENCES

1. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2001; **22**:477-501.
2. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res* 2007; **22 Suppl 2**:V28-33.
3. Lips P. Vitamin D physiology. *Prog Biophys Mol Biol* 2006; **92**:4-8.
4. Kuchuk NO, van Schoor NM, Pluijm SM, Chines A, Lips P. Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: global perspective. *J Bone Miner Res* 2009; **24**:693-701.
5. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004; **116**:634-639.
6. van Schoor NM, Visser M, Pluijm SM, *et al.* Vitamin D deficiency as a risk factor for osteoporotic fractures. *Bone* 2008; **42**:260-266.
7. Steingrimsdottir L, Halldorsson TI, Siggeirsdottir K, *et al.* Hip fractures and bone mineral density in the elderly--importance of serum 25-hydroxyvitamin D. *PLoS One* 2014; **9**:e91122.
8. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med* 2006; **166**:424-430.
9. Kalyani RR, Stein B, Valiyil R, *et al.* Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc* 2010; **58**:1299-1310.
10. Chung M, Balk EM, Brendel M, *et al.* Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess* 2009; 1-420.
11. Oosterwerff MM, Eekhoff EM, Heymans MW, Lips P, van Schoor NM. Serum 25-hydroxyvitamin D levels and the metabolic syndrome in older persons: a population-based study. *Clin Endocrinol (Oxf)* 2011; **75**:608-613.
12. Bikle DD. Extraskeletal actions of vitamin D. *Ann N Y Acad Sci* 2016; **1376**:29-52.
13. Pludowski P, Holick MF, Grant WB, *et al.* Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol* 2018; **175**:125-135.
14. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol* 2018; **175**:60-81.
15. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014; **348**:g2035.
16. Manson JE, Cook NR, Lee IM, *et al.* Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med* 2019; **380**:33-44.
17. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; **84**:18-28.
18. Sohl E, de Jongh RT, Heymans MW, van Schoor NM, Lips P. Thresholds for Serum 25(OH)D Concentrations With Respect to Different Outcomes. *J Clin Endocrinol Metab* 2015; **100**:2480-2488.
19. Kuchuk NO, Pluijm SM, van Schoor NM, *et al.* Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. *J Clin Endocrinol Metab* 2009; **94**:1244-1250.

20. Health Council of the Netherlands. Evaluation of the dietary reference values for vitamin D. Publication no. 2012/15E. Health Council of the Netherlands, The Hague, 2012
21. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D and Calcium The National Academies Collection: Reports funded by National Institutes of Health. In Ross AC, Taylor CL, Yaktine AL, Del Valle HB (eds) Dietary Reference Intakes for Calcium and Vitamin D. *National Academies Press (US), National Academy of Sciences* Washington (DC), 2011.
22. Holick MF, Binkley NC, Bischoff-Ferrari HA*, et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**:1911-1930.
23. Gutierrez OM, Farwell WR, Kermah D, Taylor EN. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos Int* 2011; **22**:1745-1753.
24. Yan L, Zhou B, Wang X*, et al.* Older people in China and the United Kingdom differ in the relationships among parathyroid hormone, vitamin D, and bone mineral status. *Bone* 2003; **33**:620-627.
25. Hannan MT, Litman HJ, Araujo AB*, et al.* Serum 25-hydroxyvitamin D and bone mineral density in a racially and ethnically diverse group of men. *J Clin Endocrinol Metab* 2008; **93**:40-46.
26. van Ballegooijen AJ, Robinson-Cohen C, Katz R*, et al.* Vitamin D metabolites and bone mineral density: The multi-ethnic study of atherosclerosis. *Bone* 2015; **78**:186-193.
27. Lee MS, Li HL, Hung TH*, et al.* Vitamin D intake and its food sources in Taiwanese. *Asia Pac J Clin Nutr* 2008; **17**:397-407.
28. Man PW, Lin W, van der Meer IM*, et al.* Vitamin D status in the Chinese population in the Netherlands: The DRAGON study. *J Steroid Biochem Mol Biol* 2016; **164**:194-198.
29. Heijboer AC, Blankenstein MA, Kema IP, Buijs MM. Accuracy of 6 routine 25-hydroxyvitamin D assays: influence of vitamin D binding protein concentration. *Clin Chem* 2012; **58**:543-548.
30. Wicherts IS, van Schoor NM, Boeke AJ*, et al.* Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007; **92**:2058-2065.
31. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. *Endocrinol Metab Clin North Am* 2010; **39**:419-446.
32. Lips P, Eekhoff M, van Schoor N*, et al.* Vitamin D and type 2 diabetes. *J Steroid Biochem Mol Biol* 2017; **173**:280-285.
33. Lu L, Yu Z, Pan A*, et al.* Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes Care* 2009; **32**:1278-1283.
34. Yin X, Sun Q, Zhang X*, et al.* Serum 25(OH)D is inversely associated with metabolic syndrome risk profile among urban middle-aged Chinese population. *Nutr J* 2012; **11**:68.
35. Pittas AG, Dawson-Hughes B, Sheehan P*, et al.* Vitamin D Supplementation and Prevention of Type 2 Diabetes. *N Engl J Med* 2019; **381**:520-530.
36. Van der Meer IM. (2010) Vitamin D deficiency in a multiethnic population; determinants, prevalence and consequences. PhD Thesis. Vrije Universiteit Amsterdam, Amsterdam
37. Burt LA, Billington EO, Rose MS*, et al.* Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. *JAMA* 2019; **322**:736-745.
38. Moayyeri A, Adams JE, Adler RA*, et al.* Quantitative ultrasound of the heel and fracture risk assessment: an updated meta-analysis. *Osteoporos Int* 2012; **23**:143-153.
39. Gonnelli S, Caffarelli C, Tanzilli L*, et al.* The association of body composition and sex hormones with quantitative ultrasound parameters at the calcaneus and phalanxes in elderly women. *Calcif Tissue Int* 2011; **89**:456-463.

40. Sohl E, de Jongh RT, Swart KM, *et al.* The association between vitamin D status and parameters for bone density and quality is modified by body mass index. *Calcif Tissue Int* 2015; **96**:113-122.
41. Zhen D, Liu L, Guan C, Zhao N, Tang X. High prevalence of vitamin D deficiency among middle-aged and elderly individuals in northwestern China: Its relationship to osteoporosis and lifestyle factors. *Bone* 2014; **71C**:1-6.
42. Huang F, Wang Z, Zhang J, *et al.* Dietary calcium intake and food sources among Chinese adults in CNTCS. *PLoS One* 2018; **13**:e0205045.
43. Kung AW, Luk KD, Chu LW, Chiu PK. Age-related osteoporosis in Chinese: an evaluation of the response of intestinal calcium absorption and calcitropic hormones to dietary calcium deprivation. *Am J Clin Nutr* 1998; **68**:1291-1297.
44. Abrams SA, O'Brien K O, Liang LK, Stuff JE. Differences in calcium absorption and kinetics between black and white girls aged 5-16 years. *J Bone Miner Res* 1995; **10**:829-833.
45. Lee WT, Leung SS, Xu YC, *et al.* Effects of double-blind controlled calcium supplementation on calcium absorption in Chinese children measured with stable isotopes (42Ca and 44Ca). *Br J Nutr* 1995; **73**:311-321.
46. Li S, He Y, Lin S, *et al.* Increase of circulating cholesterol in vitamin D deficiency is linked to reduced vitamin D receptor activity via the Insig-2/SREBP-2 pathway. *Mol Nutr Food Res* 2016; **60**:798-809.
47. Wang Y, Si S, Liu J, *et al.* The Associations of Serum Lipids with Vitamin D Status. *PLoS One* 2016; **11**:e0165157.
48. Qi D, Nie X, Cai J. The effect of vitamin D supplementation on hypertension in non-CKD populations: A systemic review and meta-analysis. *Int J Cardiol* 2016; **227**:177-186.
49. Snijder MB, van Dam RM, Visser M, *et al.* Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005; **90**:4119-4123.
50. Walsh JS, Evans AL, Bowles S, *et al.* Free 25-hydroxyvitamin D is low in obesity, but there are no adverse associations with bone health. *Am J Clin Nutr* 2016; **103**:1465-1471.
51. Konradsen S, Ag H, Lindberg F, Hexeberg S, Jorde R. Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. *Eur J Nutr* 2008; **47**:87-91.
52. Bischof MG, Heinze G, Vierhapper H. Vitamin D status and its relation to age and body mass index. *Horm Res* 2006; **66**:211-215.