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RESEARCH PAPER

Vitamin D deficiency is associated with orthostatic hypotension in older men: a cross-sectional analysis from the British Regional Heart Study

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Abstract

Background: orthostatic hypotension (OH) that occurs within, or at, 1 minute of standing is associated with higher risk of falls, myocardial infarction, syncope and mortality, compared to OH that occurs after 1 minute of standing. Whether vitamin D deficiency increases the risk of OH is controversial.
Methods: this was a cross-sectional analysis of 3,620 older, community-dwelling men. Multinomial, multiple logistic regression models were used to calculate the risk of OH across categories of vitamin D status (deficient [<25 nmol/l], insufficient [≥25–<50 nmol/l] and sufficient [≥50 nmol/l]) and parathyroid hormone quintile.
Results: men with vitamin D deficiency were more likely to have OH that occurred within 1 minute of standing in univariate logistic regression (OR 1.88, 95% CI 1.40–2.53) and multinomial, multiple logistic regression (OR 1.51, 95% CI 1.06–2.15), compared to men with sufficient levels of vitamin D. Vitamin D insufficiency was not associated with the risk of OH. Elevated parathyroid hormone was not associated with risk of OH.
Conclusion: the absence of an association between vitamin D insufficiency and risk of OH and the presence of an association between vitamin D deficiency and risk of OH suggest that there may be a threshold effect; it is only below a particular level of vitamin D that risk of OH is increased. In this cohort, the threshold was <25 nmol/l. Future work should investigate whether treating vitamin D deficiency can improve postural blood pressure or if preventing vitamin D deficiency reduces the incidence of OH.

Keywords: geriatrics, epidemiology, orthostatic hypotension, vitamin D, older people

Key Points

- Men with vitamin D deficiency had increased risk of OH that occurred within 1 minute of standing.
- Vitamin D insufficiency and elevated PTH were not statistically significantly associated with risk of OH.
- The controversy in this area of research may be explained, in part, by different definitions of vitamin D deficiency.
- Thresholds to define vitamin D deficiency may need to be disease or adverse outcome-specific.
- Interventional studies may clarify whether vitamin D supplementation can improve OH.

Introduction

Whether vitamin D deficiency increases risk of orthostatic hypotension (OH) is controversial [1–7]. Almost 1 in 3 adults >65 years old is deficient in vitamin D during the winter months in the United Kingdom [8], while OH is found in over 1 in 5 community-dwelling older adults [9]. OH increases the risk of falls, fractures, cardiovascular disease and all-cause mortality [10–12]. It is also associated with late-life depression and dementia [13,14]. OH that occurs within, or at, 1 minute of standing has been associated with higher risk of falls, myocardial infarction (MI), syncope and mortality, compared to OH that occurs after 1 minute of standing [15–17]. It is important to clarify the association between vitamin D deficiency and OH because current treatment options for OH are limited, and vitamin D supplements are cheaply and widely available.

Smaller studies suggest that lower levels of circulating vitamin D are associated with increased risk of OH [1–3,5,7], while larger studies do not [6,18], and the current evidence base has specific limitations. Firstly, not all of the studies controlled for parathyroid hormone (PTH). PTH and vitamin D work in concert, through feedback cycles [19], so PTH may mediate, or confound, the association between vitamin D and OH. Secondly, men have been underrepresented in the current evidence base: only 27% of those with low circulating vitamin D in a systematic review and meta-analysis investigating the association between circulating vitamin D and OH were men [4]. Thirdly, few studies have examined whether vitamin D status relates to the timeframe within which OH occurs [6,18]. Finally, none of the available studies have investigated a UK-based cohort. This is relevant because circulating vitamin D concentration is determined by dietary sources and synthesis in the skin via exposure to ultraviolet radiation [20], factors that are geographically dependent [21]. Therefore, the external validity of the currently available data is limited.

In this cross-sectional study, we aimed to address these issues by exploring the association between circulating vitamin D, PTH and OH in older, community-dwelling, men.

Methods

Study population

This analysis was based on data from the 20th year rescreen of participants of the British Regional Heart Study. Sampling methods have been described previously [22]. The British Regional Heart Study is an on-going prospective cohort study that first recruited 7,735 men, aged 40–59 years, between 1978 and 1980, from one general practice in each of 24 British towns. The sample was socioeconomically representative of the population. Participants were predominantly (>99%) of white European ethnicity. For the 20th year rescreen, all surviving men were invited for reexamination that took place between 1998 and 2000. A total of 4,252 men completed a self-administered questionnaire and underwent physical examination (77% response rate) [22, 23]. Ethical approval was obtained from the National Research Ethics Service Committee London.

A total of 3,799 men had a vitamin D measurement, and 109 men with prevalent heart failure were excluded because heart failure is strongly associated with hypertension [24], a major determinant of OH [25–28], and because of their exceptionally high risk of mortality [29]. A total of 67 participants with incomplete sitting and standing blood pressure (BP) measurements were also excluded. We further excluded two men with PTH measurements >200 pg/ml, as these measurements likely reflected a specific disease such as hyperparathyroidism, and one man with a circulating vitamin D level >250 nmol/l. Thus, 3,620 participants were left for analysis. Of these, 3,618 had PTH measurements.

Vitamin D and PTH measurements

A fasting blood sample was taken on the same day as the physical examination. Total vitamin D ($25OHD_2$ plus $25OHD_3$; referred to here as 'vitamin D') was measured using a gold-standard liquid chromatography–tandem mass spectrometry method following an automated solid-phase extraction procedure [30]. Measurements were made in ng/ml and converted into nmol/l. The lower limit of sensitivity was 10 nmol/l. PTH was measured by electrochemiluminescence using a clinically validated assay for intact PTH [30].

BP measurement

BP measurements were taken on the right arm using an automatic Dinamap 1846SX. The Dinamap BP monitor overestimated systolic BP by ~8 mmHg compared with the standard mercury sphygmomanometer that was the standard reference instrument for BP measurement at the time [31]. 8 mmHg was therefore subtracted from raw systolic BP readings. Cuff size was selected in accordance with arm circumference: a standard adult cuff if the arm circumference was between 28.0 cm and 35.0 cm, a small adult cuff if it was <28.0 cm and a large adult cuff if it was >35.0 cm. For sitting measurements, participants were asked to rest their arm on the examination table, such that the upper arm was at chest level. During measurements, participants were discouraged from talking and encouraged to keep the arm still.

The Dinamap was set to take repeated measurements at 1 minute intervals. Four consecutive BP measurements were taken: two sitting, followed by two standing. Participants had not been seated, nor supine, for a prescribed duration prior to the first sitting measurement. After the second sitting measurement completed, the participant was asked to stand up (at least 1 minute and 30 seconds after sitting down for

the first BP measurement). The first standing BP measurement began within 1 minute of the participant standing. The second standing BP measurement began after 1 minute of standing.

Definition of OH

'Consensus OH' was defined by consensus [32] as a decrease in systolic BP ≥20 mmHg and/or diastolic BP ≥10 mmHg that occurred between either the first, or second, standing BP measurements and the mean of the two preceding sitting BP measurements. Consensus OH was subdivided, based on the timeframe within which it occurred, into OH-1 and OH-2. OH-1 was OH that occurred within 1 minute of standing, regardless of whether it persisted or corrected during the second minute of standing; OH-2 was OH that only occurred during the second minute of standing.

Statistical methods

Statistical analyses were performed using SAS 9.4. Vitamin D status was categorized as per the United Kingdom's National Institute for Health and Care Excellence Clinical Knowledge Summaries [33]: deficient (<25 nmol/l), insufficient (≥25–<50 nmol/l) or sufficient (≥50 nmol/l). The 'sufficient' group was the reference group for hypothesis testing. In the case of PTH, participants were divided into quintiles. The first (lowest) quintile was the reference group. Comparisons of baseline characteristics were performed using the chi-square test for categorical variables and generalized linear models for continuous variables.

Loess regression was used to plot the curves for the association between probability of OH and circulating vitamin D and PTH. Logistic regression was used to assess the association between vitamin D status and OH, and PTH quintile and OH. Multinomial logistic regression was used to examine the association between vitamin D status and timeframe of OH (OH-1 and OH-2). The reference group ('No OH') consisted of participants who had neither OH-1 nor OH-2. Age, body mass index (BMI), resting pulse, systolic BP, total cholesterol, PTH and IL-6 were fitted as continuous variables in the multiple regression models. Categorical covariates were smoking status (never smoked, ex-smoker for 0–15 years, ex-smoker for >15 years and current smoker), alcohol use (0–15 units/week and >16 units/week), season in which blood samples for vitamin D measurement were taken (spring, summer, autumn or winter), physical activity (active or inactive), physical disability (no disability, mild disability or moderate disability), self-reported vitamin D or multivitamin supplementation (taking supplementation or not taking supplementation), social class (manual or nonmanual) and the presence of prevalent stroke, MI, atrial fibrillation (AF), diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and current antihypertensive medication use.

Case definitions of MI, stroke and diabetes were obtained from primary care record reviews [34]. AF was defined according to Minnesota codes 8.3.1 and 8.3.3. Hypertension was defined as mean sitting systolic BP ≥140 mmHg and/or mean sitting diastolic BP ≥90 mmHg and/or antihypertensive medication use. Antihypertensive medication use was based on self-report and defined as use of any antihypertensive medication as per British National Formulary (version 38) code 3.1. CKD was defined as an estimated glomerular filtration rate <60 ml/minute/1.73 m^2, as estimated from serum creatinine using the Modification of Diet in Renal Disease equation [35]. 'Inactive' was defined as inactivity or occasional physical activity based on self-reported questionnaire data. Definitions of physical disability were based on self-reported questionnaire responses to questions regarding difficulty going up or down stairs and difficulty walking for a quarter of a mile on the level. 'No disability' was if participants did not have difficulty with either, 'mild disability' if they reported difficulty with one or the other and 'moderate disability' if they reported difficulty with both. Methods of measurement and classification for measures of lipids, lung function, smoking status, physical activity, alcohol intake and social class have been described previously [36, 37].

Results

Among 3,620 community-dwelling men (mean age 68.6 years, SD 5.5 years), 10% had vitamin D deficiency. Men with vitamin D deficiency tended to have the most adverse characteristics (Table 1). They were older, more likely to be current smokers, inactive, disabled and had the highest prevalence of stroke, diabetes, COPD and antihypertensive medication use. They had the highest mean levels of resting pulse, sitting systolic BP, CRP, IL-6 and PTH.

There was a nonlinear association between probability of consensus OH and circulating vitamin D level, suggestive of a threshold effect occurring at a level below approximately 40 nmol/l, where probability of OH increased (Figure 1A). Higher concentration of PTH correlated with increased probability of consensus OH (Figure 1B).

Vitamin D status and risk of OH

Consensus OH was found in 26.5, 19.6 and 18.6% of those with vitamin D deficiency, vitamin D insufficiency and sufficient circulating vitamin D, respectively (Table 2). Compared to men with sufficient circulating vitamin D, only men with vitamin D deficiency had statistically significantly increased risk of consensus OH (OR 1.57, 95% CI 1.21–2.05). This association was markedly attenuated, and not statistically significant, in multiple logistic regression analysis (OR 1.31, 95% CI 0.96–1.78) (Table 2). When consensus OH was divided into its components based on

Table 1. Baseline characteristics of the study population stratified by vitamin D status (nmol/l)

	Deficient: <25 (n = 363)	Insufficient: ≥25–<50 (n = 1,533)	Sufficient: ≥50 (n = 1724)	
Anthropometric measurements	Mean (SD)			P
Age, years	69.3 (5.7)	68.7 (5.5)	68.4 (5.4)	0.0064
BMI, kg/m^2	26.8 (4.5)	27.1 (3.8)	26.6 (3.3)	0.0003
Waist circumference, cm	98.3 (12.5)	97.8 (10.6)	96.0 (9.5)	<0.0001
Sitting systolic BP, mmHg	152.6 (26.5)	148.7 (24.1)	149.1 (23.6)	0.0207
Sitting diastolic BP, mmHg	84.9 (12.1)	85.1 (11.3)	85.4 (10.8)	0.5148
Heart rate, beats per minute	68 (13)	66 (13)	65 (12)	<0.0001
Arm circumference, cm	30.0 (3.4)	30.5 (2.9)	30.3 (2.6)	0.0266
Biochemical measurements	Mean (SD)			
CRP[a], mg/l	2.3 (1.0–5.1)	1.7 (0.9–3.4)	1.6 (0.8–3.1)	<0.0001
IL-6[a], mg/l	3.0 (1.8–4.4)	2.5 (1.6–3.6)	2.2 (1.5–3.1)	<0.0001
PTH[a], pg/ml	53.5 (41.3–69.4)	46.5 (38.1–57.4)	42.1 (33.8–51.9)	<0.0001
Cholesterol, mmol/l	5.8 (1.1)	6.0 (1.1)	6.0 (1.1)	0.0046
HDL, mmol/l	1.3 (0.4)	1.3 (0.4)	1.3 (0.3)	0.0909
Phosphate, mmol/l	1.2 (0.2)	1.2 (0.2)	1.2 (0.2)	0.8599
Calcium, mmol/l	2.3 (0.1)	2.3 (0.1)	2.4 (0.1)	0.0783
Vitamin D, nmol/l	16.9 (5.5)	37.0 (6.9)	69.0 (17.2)	<0.0001
Co-morbid conditions (n, %)				
Hypertension	284 (78.2)	1,142 (74.5)	1,285 (74.6)	0.3044
MI	31 (8.5)	94 (6.1)	104 (6.0)	0.1872
Stroke	20 (5.5)	47 (3.1)	38 (2.2)	0.0026
AF	18 (5.0)	53 (3.5)	49 (2.9)	0.1151
Diabetes	29 (8.0)	102 (6.7)	79 (4.6)	0.0071
CKD	50 (13.8)	219 (14.4)	247 (14.4)	0.9545
Antihypertensive use	131 (36.1)	476 (31.1)	509 (29.5)	0.0478
COPD	123 (35.1)	407 (26.7)	418 (24.4)	0.0002
Lifestyle, physical disability and social class (n, %)				
Current smokers	91 (25.1)	200 (13.1)	168 (9.8)	<0.0001
Moderate to heavy alcohol consumption	80 (22.7)	290 (19.2)	332 (19.5)	0.3253
Inactive	195 (56.9)	515 (34.8)	469 (28.1)	<0.0001
Physical disability	55 (15.2)	131 (8.6)	133 (7.7)	<0.0001
Manual social class	192 (53.2)	779 (50.9)	886 (51.5)	0.7220
Vitamin D/calcium supplementation and season of examination (n, %)				
Vitamin D supplements	10 (2.8)	66 (4.3)	169 (9.8)	<0.0001
Calcium supplements	3 (0.8)	14 (0.9)	16 (0.9)	0.9830
Spring	114 (31.4)	410 (26.7)	266 (15.4)	<0.0001
Summer	72 (19.8)	309 (20.2)	555 (32.2)	
Autumn	59 (16.3)	389 (25.4)	624 (36.2)	
Winter	118 (32.5)	425 (27.7)	279 (16.2)	

[a]Geometric mean (interquartile range)

timeframe, in multinomial, multiple logistic regression analysis that included PTH and co-morbidities as covariates, there was a statistically significant association between vitamin D deficiency and OH-1 (OR 1.51, 95% CI 1.06–2.15) but not OH-2. Vitamin D insufficiency was not statistically significantly associated with OH-1 or OH-2 (Table 2).

PTH and risk of OH

After adjustment for age, BMI, resting pulse and mean sitting systolic BP, there was no statistically significantly increased risk of consensus OH, OH-1 or OH-2 in participants with elevated PTH levels (Table 3).

Discussion

In this cross-sectional study of older, community-dwelling men, vitamin D deficiency was associated with increased risk of OH that occurred within 1 minute of standing. No association was seen between vitamin D insufficiency and risk of OH or elevated PTH and risk of OH, regardless of the timeframe within which OH occurred. The association between vitamin D deficiency and OH was independent of BP and PTH. The vitamin D receptor is found in cardiomyocytes and vascular endothelial cells [38], vitamin D deficiency may contribute to endothelial dysfunction [39] and upregulation of the renin-angiotensin-aldosterone system [40], and vitamin D itself may promote vascular

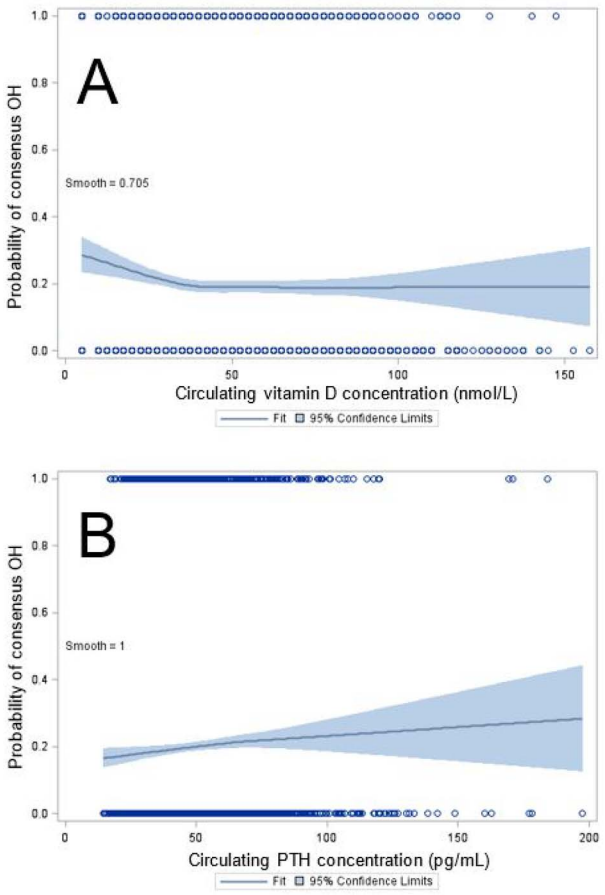

Figure 1. Fit plots generated through loess regression for the probability between OH and vitamin D (A) and OH and PTH (B).

regeneration after injury [41]. Hence, there may be a speculative, but biologically plausible, mechanism that may underlie the observed association.

Smaller studies have reported an association between vitamin D status and OH [1–3,5,7], while larger studies have not [6,18]. The inconsistencies may be explained by different definitions of vitamin D deficiency, different reference groups and different definitions of OH, with respect to the timeframe within which OH occurs (Table 4). Indeed, we detected a statistically significant association between vitamin D deficiency and OH-1, but not OH-2. Furthermore, when we reanalyzed our data with <30 nmol/l as the cut-off to define vitamin D deficiency (data not shown), there was no statistically significant association between vitamin D deficiency and OH, irrespective of timeframe. In one randomized controlled trial, vitamin D supplementation did not result in a statistically significant improvement in OH [42]. However, the sample size limited the size of the reduction in OH that could have been detected.

The definition of vitamin D deficiency remains controversial [43]; the United Kingdom's National Institute for Health and Care Excellence Clinical Knowledge Summaries defines it as <25 nmol/l [33], while the United States' Institute of Medicine defines it as <30 nmol/l [44]. The cut-offs may need to be disease and/or adverse-outcome specific; our findings suggest a cut-off of <25 nmol/l is associated with risk of OH, while a cut-off of <30 nmol/l is not, i.e. only those with extremely low circulating vitamin D concentrations are at increased risk of OH.

Strengths of our study include the large sample size, a gold standard measurement of vitamin D and that we examined PTH, alongside a wide range of other possible confounders or mediators. Limitations include, firstly, that men with OH were identified based on sitting and standing BP measurements, rather than lying and standing measurements. We used the thresholds that are ordinarily used for lying and standing measurements to identify men with OH, as the optimal thresholds to diagnose OH based on sitting and standing measurements are not known. If these thresholds are lower than those for lying and standing measurements, then we would have underestimated the proportion of men with OH. Further factors that may have reduced detection of OH include the men not being seated for a prescribed duration prior to the first BP measurement and using an automatic BP monitor to measure BP, rather than taking continuous beat-to-beat BP measurements. Secondly, we did not have data on diagnosis of Parkinson's disease, a neurodegenerative condition in which OH is often found, and are unable to exclude this as a confounding factor. Thirdly, although we adjusted for antihypertensive medications, we did not adjust for other drugs that may cause OH, such as antipsychotics, antidepressants or opioids. Fourthly, 424 men did not have a vitamin D measurement and were excluded from the sample. However, there was no statistically significant difference in age, physical disability and in proportion of people with OH between these men and those who had vitamin D measurements. Therefore, their exclusion was unlikely to bias the findings. Fifthly, although we controlled for physical disability, we were unable to control specifically for frailty, which is associated with both vitamin D [45] and OH [46], and therefore cannot exclude the possibility of residual confounding. Sixthly, all of our participants were men, and the vast majority (>99%) were of white European ethnicity; the generalizability of our findings is restricted. Finally, this study was cross-sectional; we are unable to comment on temporality and causation.

In conclusion, vitamin D deficiency increased odds of OH that occurred within 1 minute of standing in this cohort of older men. Risk of OH increased only below a particular threshold of circulating vitamin D (<25 nmol/l). Prospective studies specifically looking at threshold effects and the significance of timeframe of OH are required to assess whether vitamin D deficiency precedes OH. Interventional studies may clarify whether vitamin D supplementation could be an effective preventative measure against OH, or whether it may be a treatment option for those who have OH.

Table 2. Odds of prevalent OH stratified by vitamin D status (nmol/l)

	Model	Deficient: <25 (n = 363)	Insufficient: ≥25–<50 (n = 1,533)	Sufficient: ≥50 (n = 1,724)	P (trend)
OH-C, n (%)		96 (26.45)	300 (19.57)	321 (18.62)	
	1	1.57 (1.21–2.05)	1.06 (0.89–1.27)	1.00	0.0049
	2	1.48 (1.13–1.94)	1.03 (0.86–1.24)	1.00	0.0231
	3	1.29 (0.95–1.75)	1.02 (0.84–1.23)	1.00	0.1977
	4	1.31 (0.96–1.78)	1.00 (0.82–1.21)	1.00	0.2294
OH-1, n (%)		73 (20.11)	196 (12.79)	204 (11.83)	
	1	1.88 (1.40–2.53)	1.09 (0.89–1.35)	1.00	0.0005
	2	1.8 (1.33–2.45)	1.08 (0.87–1.34)	1.00	0.0016
	3	1.56 (1.10–2.20)	1.09 (0.87–1.38)	1.00	0.0278
	4	1.51 (1.06–2.15)	1.05 (0.83–1.33)	1.00	0.0617
OH-2, n (%)		23 (6.34)	104 (6.78)	117 (6.79)	
	1	1.03 (0.65–1.65)	1.01 (0.77–1.33)	1.00	0.8893
	2	0.94 (0.58–1.51)	0.95 (0.71–1.26)	1.00	0.6990
	3	0.86 (0.52–1.43)	0.89 (0.66–1.20)	1.00	0.4228
	4	0.94 (0.56–1.59)	0.91 (0.67–1.23)	1.00	0.6221

Model 1: unadjusted. Model 2: age- and season-adjusted. Model 3 = Model 2 plus BMI, heart rate, mean sitting systolic BP, total cholesterol, smoking, alcohol consumption, physical activity, social class, vitamin D supplementation, prevalent stroke, MI, AF, diabetes, antihypertensive medication use, CKD and COPD. Model 4 = Model 3 plus physical disability, PTH and IL-6. 'OH-C' is consensus OH; 'OH-1' is OH occurring within 1 minute of standing; 'OH-2' is OH occurring after 1 minute of standing. The given P-value is the P for trend

Table 3. Odds of prevalent OH between quintiles of PTH level

	PTH Quintile (pg/ml)						
	Model	Q1: ≤34.2 (n = 727)	Q2: >34.2–≤41.2 (n = 723)	Q3: >41.2–≤48.8 (n = 721)	Q4: >48.8–≤59.2 (n = 721)	Q5: >59.2 (n = 726)	P (trend)
OH-C, n (%)		119 (16.37)	144 (19.92)	145 (20.11)	153 (21.22)	154 (21.21)	
	1	1.00	1.27 (0.97–1.66)	1.29 (0.98–1.68)	1.38 (1.06–1.8)	1.38 (1.06–1.79)	0.0188
	2	1.00	1.25 (0.96–1.64)	1.27 (0.97–1.66)	1.33 (1.02–1.73)	1.3 (0.99–1.69)	0.0635
	3	1.00	1.24 (0.94–1.64)	1.20 (0.91–1.59)	1.25 (0.95–1.65)	1.13 (0.86–1.49)	0.4655
OH-1, n (%)		80 (11)	90 (12.45)	93 (12.90)	94 (13.04)	115 (15.84)	
	1	1.00	1.18 (0.86–1.63)	1.23 (0.89–1.69)	1.26 (0.91–1.73)	1.53 (1.12–2.08)	0.0085
	2	1.00	1.16 (0.84–1.60)	1.21 (0.88–1.67)	1.21 (0.88–1.66)	1.43 (1.05–1.95)	0.0311
	3	1.00	1.15 (0.83–1.61)	1.14 (0.82–1.59)	1.14 (0.82–1.58)	1.25 (0.91–1.72)	0.2261
OH-2, n (%)		39 (5.36)	54 (7.47)	52 (7.21)	59 (8.18)	39 (5.37)	
	1	1.00	1.45 (0.95–2.23)	1.41 (0.92–2.16)	1.62 (1.06–2.47)	1.06 (0.67–1.68)	0.6030
	2	1.00	1.44 (0.94–2.20)	1.39 (0.91–2.15)	1.58 (1.03–2.40)	1.02 (0.64–1.61)	0.7624
	3	1.00	1.42 (0.93–2.19)	1.32 (0.85–2.04)	1.49 (0.97–2.27)	0.88 (0.55–1.40)	0.6956

Model 1: unadjusted. Model 2: age-adjusted. Model 3: adjusted for age, BMI, resting pulse and mean sitting systolic BP. 'OH-C' is consensus OH; 'OH-1' is OH occurring within 1 minute of standing; 'OH-2' is OH occurring after 1 minute of standing. The given P-value is the P for trend

Table 4. Comparison of cut-offs used to define vitamin D deficiency, reference groups and time point(s) after standing at which BP measurements were taken to assess for OH in different studies

Study	Design	n	Age (years)	Cut-off defining vitamin D deficiency or hypovitaminosis D (nmol/l)	Cut-off defining reference group (nmol/l)	Time point(s) after standing when BP was measured	Association between vitamin D and OH
McCarroll *et al*. [3]	Case-control	76	≥64[a]	Continuous	N/A	Every 30 seconds, continuing until 3 minutes had elapsed	Present
Annweiler *et al*. [1]	Cross-sectional	329	80–94.3	≤25	>25	A single measurement within 3 minutes of standing (specific time point not specified)	Present
Soysal *et al*. [5]	Retrospective	546	≥65[a]	<50	≥50	At 1 and 3 minutes	Present
Veronese *et al*. [6]	Cross-sectional	2,640	65–98	≤25	>75	After 1 and 3 minutes	Not present
Duval *et al*. [2]	Prospective	51	82[b]	≤25	Not specified	After 3 minutes	Present
Veronese *et al*. [7]	Prospective	1,308	65–93	≤69 in men; ≤42 in women (cut-offs based on quartiles)	>142 in men; >92 in women	After 1 and 3 minutes	Present (not statistically significant in men)
Laird *et al*. [18]	Cross-sectional	4,209	>50[a]	<30	≥50	Up to 40 seconds and throughout 110 seconds poststand	Not present

Age range not specified: [a]lower limit for inclusion; [b]mean age at base line

Declaration of Conflicts of Interest: None.

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