Abstract

Background
Orthostatic hypotension that occurs within, or at, one minute of standing is associated with higher risk of falls, myocardial infarction, syncope and mortality, compared to orthostatic hypotension that occurs after one minute of standing. Whether vitamin D deficiency increases risk of orthostatic hypotension is controversial.

Methods
This was a cross-sectional analysis of 3620 older, community-dwelling men. Multinomial, multiple logistic regression models were used to calculate risk of orthostatic hypotension 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 orthostatic hypotension that occurred within one 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 risk of orthostatic hypotension. Elevated parathyroid hormone was not associated with risk of orthostatic hypotension.

Conclusion
The absence of an association between vitamin D insufficiency and risk of orthostatic hypotension, and presence of an association between vitamin D deficiency and risk of orthostatic hypotension, suggests there may be a threshold effect; it is only below a particular level of vitamin D that risk of orthostatic hypotension 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 orthostatic hypotension.

Introduction

Whether vitamin D deficiency increases risk of orthostatic hypotension (OH) is controversial [1-7]. Almost 1 in 3 adults >65 years old are 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 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, one minute of standing has been associated with higher risk of falls, myocardial infarction, syncope and mortality, compared to OH that occurs after one 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 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 re-screen of participants of The British Regional Heart Study (BRHS). Sampling methods have been described previously [22]. The BRHS is an on-going prospective cohort study that first recruited 7735 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 re-screen, all surviving men were invited for re-examination that took place between 1998 and 2000. 4252 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.

3799 men had a vitamin D measurement. 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]. 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, 3620 participants were left for analysis. Of these, 3618 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 (25OHD2 plus 25OHD3; 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. An adult cuff was used if the arm circumference was <32 cm; a large adult cuff if it was ≥32 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 one 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 blood pressure measurement). The first standing BP measurement began within one minute of the participant standing. The second standing BP measurement began after one 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 sub-divided, based on the timeframe within which it occurred, into OH-1 and OH-2. OH-1 was OH that occurred within one 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 categorised as per the United Kingdom’s National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries (CKS) [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 generalised 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 non-manual) and the presence of prevalent stroke, myocardial infarction (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/min/1.73m2, 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 3620 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 non-linear 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 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 blood pressure, 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 one 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 blood pressure 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 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 re-analysed 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 randomised 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 NICE CKS 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 blood pressure measurements, rather than lying and standings 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 blood pressure measurement and using an automatic blood pressure monitor to measure blood pressure, rather than taking continuous beat-to-beat blood pressure 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 anti-hypertensive medications, we did not adjust for other drugs that may cause OH, such as anti-psychotics, anti-depressants or opiods. 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 generalisability 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 one 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.

Conflict(s) of Interest/Disclosure(s)
None

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



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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Deficient:** **<25 (n=363)** | **Insufficient:** **≥25 - <50 (n=1533)** | **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/m2 | 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) | **<.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) | **<.0001** |
| Arm circumference, cm | 30.0 (3.4) | 30.5 (2.9) | 30.3 (2.6) | **0.0266** |
| **Biochemical Measurements** | **Mean (SD)** |  |
| CRP\*, mg/L | 2.3 (1.0 - 5.1) | 1.7 (0.9 - 3.4) | 1.6 (0.8 - 3.1) | **<.0001** |
| IL-6\*, mg/L | 3.0 (1.8 - 4.4) | 2.5 (1.6 - 3.6) | 2.2 (1.5 - 3.1) | **<.0001** |
| PTH\*, pg/mL | 53.5 (41.3 - 69.4) | 46.5 (38.1 - 57.4) | 42.1 (33.8 - 51.9) | **<.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) | **<.0001** |
| **Co-morbid Conditions (n, %)** |  |  |  |  |
| Hypertension | 284 (78.2) | 1142 (74.5) | 1285 (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 |
| Anti-hypertensive 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) | <.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) | <.0001 |
| Physical disability | 55 (15.2) | 131 (8.6) | 133 (7.7) | <.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) | <.0001 |
| Calcium supplements | 3 (0.8) | 14 (0.9) | 16 (0.9) | 0.9830 |
| Spring | 114 (31.4) | 410 (26.7) | 266 (15.4) | <.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) |

\* = Geometric mean (interquartile range).

Table 2: Odds of prevalent OH stratified by vitamin D status (nmol/L)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Model** | **Deficient:** **<25 (n=363)** | **Insufficient:** **≥25 - <50 (n=1533)** | **Sufficient: ≥50 (n=1724)** | **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, anti-hypertensive 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 one minute of standing; “OH-2” is OH occurring after one 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 blood pressure. “OH-C” is consensus OH; “OH-1” is OH occurring within one minute of standing; “OH-2” is OH occurring after one 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 blood pressure 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 blood pressure was measured | Association between vitamin D and OH |
| McCaroll et al. (3) | Case-control | 76 | ≥64\* | 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\* | <50 | ≥50 | At 1 and 3 minutes | Present |
| Veronese et al. (6) | Cross-sectional | 2640 | 65 - 98 | ≤25 | >75  | After 1 and 3 minutes | Not present |
| Duval et al. (2) | Prospective | 51 | 82†  | ≤25   | Not specified | After 3 minutes | Present |
| Veronese et al. (7) | Prospective | 1308 | 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 | 4209 |  >50\* | <30 | ≥50 | Up to 40 seconds and throughout 110 seconds post-stand | Not present |

Age range not specified: \*lower limit for inclusion; † mean age at baseline