

Orthostatic Hypotension

Vitamin D Status Is Not Associated With Orthostatic Hypotension in Older Adults

Eamon J. Laird, Triona McNicholas, Aisling M. O'Halloran, Martin Healy, Anne M. Molloy, Daniel Carey, Deirdre O'Connor, Kevin McCarroll, Rose Anne Kenny

Abstract—There has been much interest in investigating vitamin D status with orthostatic hypotension. However, studies have been small, inconsistent, and with a lack of standardization. The aim of this study was to investigate the association with vitamin D status in a large, nationally representative older adult population using a traceable standard of measurement and an accurate assessment of beat-to-beat blood pressure (BP). This study used participants aged >50 years from The Irish Longitudinal Study on Ageing. Impaired stabilization of BP on standing was defined as a sustained drop of ≥ 20 mmHg systolic BP or ≥ 10 mmHg diastolic BP up to 40 seconds post stand (impaired stabilization of BP on standing). We also analyzed participants who sustained a drop of ≥ 20 mmHg systolic BP or ≥ 10 mmHg diastolic BP throughout the 110 seconds stand (OH110). Vitamin D was categorized into sufficient (≥ 50 nmol/L), insufficient (30–50 nmol/L), and deficient (<30 nmol/L) status. After exclusion criteria 4209 participants were included. Those with deficiency were more likely to be smokers, take antihypertensive medications and had higher levels of cardiovascular disorders compared with those with sufficient status. In a univariate logistic regression those with deficient (odds ratio, 1.18; 95% CI, 0.86–1.61; $P=0.303$) or insufficient (odds ratio, 1.13; 95% CI, 0.91; $P=0.272$) status were no more likely to have evidence of impaired stabilization of BP on standing on active stand compared with sufficiency. Similar findings were found for OH110: deficient (odds ratio, 0.85; 95% CI, 0.52–1.40; $P=0.528$) or insufficient (odds ratio, 0.86; 95% CI, 0.61–1.21; $P=0.384$) versus sufficiency. In conclusion, vitamin D is not significantly associated with orthostatic hypotension in older adults. (*Hypertension*. 2019;74:639–644. DOI: 10.1161/HYPERTENSIONAHA.119.13064.) • [Online Data Supplement](#)

Key Words: adult ■ aging ■ blood pressure ■ hypotension ■ vitamin D

Orthostatic hypotension (OH) is an increasingly common chronic condition estimated to affect 30% of all older community-dwelling adults (≥ 65 years).¹ It is typically characterized as a significant drop in blood pressure (BP) on standing and is associated with adverse health outcomes, including increased risk of falls, fracture, cardiovascular events, and all-cause mortality.^{2–4} The mainstay of treatment for OH involves nonpharmacological methods, including increasing fluid and salt intake, compression hosiery, and physical counter maneuvers.⁵ In some cases, for example, those with OH secondary to neurodegenerative diseases such as Parkinson disease and multiple system atrophy, treatment of OH may include of medications, such as midodrine, fludrocortisone, and droxidopa. These drugs can have adverse side effects, and the efficacy of a pharmacological treatment approach has been questioned.⁵ While such groups may require pharmacological treatment, there is a constant search for simple modifiable risk factors with a minimal risk of adverse effects which can have sustained benefits as part of a treatment regime. Recently, nutritional status has been proposed as a modifiable risk factor with a particular emphasis on vitamin D.⁶

Vitamin D is a secosteroid hormone primarily synthesized following dermal exposure to ultraviolet B light but can also be partially obtained from dietary sources including oily fish and fortified food products and supplements.^{7,8} However, at far latitudes meaningful productive synthesis is limited to the summer months. Furthermore, vitamin D rich foods are infrequently consumed in the Western diet.^{7,8} This unfortunate combination of inadequate production and intakes is further compounded by the multitude of factors which can impede vitamin D synthesis/metabolism, such as body mass index (BMI), sunscreen use, pollution, ethnicity, choice of clothing, older age, etc.⁷ It is, therefore, unsurprising that high rates of vitamin D deficiency (defined as a 25-hydroxyvitamin D [25(OH)D] concentration <30 nmol/L⁹) have been reported.¹⁰ Substantial evidence exists for the beneficial effects of vitamin D for bone and musculoskeletal health, although the evidence for extraskeletal outcomes, such as reduction of cancer or cardiovascular disease risk, is considerably weaker.⁹ Among the purported extraskeletal health outcomes, vitamin D has been associated with OH in some but not all studies (Table S1 in the [online-only Data Supplement](#)).^{11–20} The exact mechanism

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From the Department of Medical Gerontology, The Irish Longitudinal Study on Ageing (TILDA), Lincoln Gate, Trinity College, Dublin, Ireland (E.J.L., T.M., A.M.O., D.C., C.O., R.A.K.); Department of Biochemistry, St James's Hospital, Dublin, Ireland (M.H.); School of Medicine, Trinity College Dublin, Ireland (A.M.M.); and Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland (K.M., R.A.K.).

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Correspondence to Eamon J. Laird, St James's Hospital, 1st Floor Research Wing, MISA Bldg, Dublin 8, Ireland. Email lairdea@tcd.ie

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is unknown, although it could be through the effect of vitamin D on the baroreflex neural arc or on the genetic expression of neurotrophins and neurotransmitters.¹² In a recent systematic review (subject n=3646), it was reported that having a low vitamin D status is associated with approximately double odds of having OH.⁶ However, there are concerns about the validity of the association of vitamin D and OH. For instance, of the 10 studies which have examined this hypothesis, 4 have had <100 participants.^{11,15–17} Furthermore, studies were conducted in different population subsets and not all have used the same cut-offs for describing low vitamin D status. Only one study¹⁷ used the recommended gold standard liquid chromatography-mass spectrometry methodology for 25(OH)D measurement while 2 studies did not report the type of assay used.^{18,20} Only one¹⁵ reported the use of an external assay validation while half of all studies did not report any precision data.^{11,13,16,18,20} It is known that discrepancies in vitamin D status occur depending on the methods used, which can result in an over/underestimation of 25(OH)D concentration and deficiency prevalence.^{9,21} Further complicating the complexity of the vitamin D-OH association is a sole randomized controlled trial that reported 12 months of high-dose vitamin D₃ supplementation did not improve OH.¹⁵

Thus, the aim of this study is to investigate the association of OH with vitamin D using evidence-based cutoffs for vitamin D status⁹ in a large, nationally representative older adult population (n >4000, aged >50 years). The study uses an internationally approved reference standard of 25(OH)D measurement (liquid chromatography-mass spectrometry) and an accurate assessment of beat-to-beat BP assessment to characterize OH.

Materials and Methods

Ethics

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants gave informed written consent. All experimental procedures adhered to the Declaration of Helsinki, and all assessments were performed by trained research nurses. Anonymized data and materials have been made publicly available at the Irish Social Science Data Archive based in University College Dublin and the Interuniversity Consortium for Political and Social Research based in the University of Michigan and can be accessed at <http://www.tilda.ie>.

Study Population

Analysis was conducted on data from wave 1 (June 2009–June 2011) of the TILDA (The Irish Longitudinal Study on Ageing), a nationally representative cohort of community-dwelling adults aged ≥50 years. Full details of the study design, sampling, and methodology have been published previously.²² In brief, the study consisted of (1) a computer-aided personal interview performed by trained interviewers in the participant's home, (2) a self-completion questionnaire, and (3) a health assessment performed by research nurses in one of 2 health centers. This study included all participants over the age of 50 who attended the health center. Participants who did not attend a health assessment, did not consent or provide a sufficient blood sample, had inadequate active stand data for analysis (signal or measurement error) or had missing data on covariates were excluded from the study.

Assessment of 25(OH)D

A nonfasting blood sample was collected by venipuncture into one 10 mL K₂EDTA tube (BD, Becton, Dickinson Limited, Oxford, United Kingdom) by a trained phlebotomist. Samples were kept chilled and

centrifuged (3000 rpm for 15 minutes), and aliquots were labeled and stored at –80°C until required for analysis. Samples for vitamin D analysis included total plasma 25(OH)D (D₂ and D₃) concentrations, which were quantified by a validated method (Chromsystems Instruments and Chemicals GmbH; MassChrom 25-OH-Vitamin D3/D2) using liquid chromatography-mass spectrometry (API 4000; AB SCIEX) and batch analyzed in the Biochemistry Department of St James's Hospital Dublin (which is accredited to ISO 15189 standard). The interassay and intraassay coefficient of variations were 5.7% and 4.5%.¹⁰ The quality of the method was monitored by the use of internal quality controls, the use of the National Institute of Standards and Technology 972 vitamin D standard reference material and with continuous participation in the vitamin D External Quality Assessment Scheme. Vitamin D was categorized according to the Institute of Medicine guidelines into sufficient (≥50 nmol/L), insufficient (30–50 nmol/L), and deficient (<30 nmol/L).⁹

Assessment of OH

Participants who attended the health center for assessment underwent an active stand, which noninvasively measures beat-to-beat BP response to stand following 10 minutes of supine rest, using digital photoplethysmography (Finometer MIDI device; Finapres Medical Systems). All recorded readings occurred in a silent room maintained at an ambient temperature of 21°C to 23°C under the supervision of a trained health nurse. Baseline BP was measured as the mean value between 60 and 30 seconds before standing during the rest period. BP was measured up to 110 seconds post stand, and estimated at 10-second intervals, using 5 seconds moving averages around each time point. Two measurements of BP response to stand were assessed in this study. Previous analysis of the TILDA data has shown that the majority of the TILDA population stabilized their BP within 40 seconds of stand,²² and therefore impaired stabilization of BP was defined as a sustained drop of ≥20 mm Hg systolic BP or ≥10 mm Hg diastolic BP up to 40 seconds post stand (impaired stabilization of BP on standing [ISBP]). We also analyzed participants who sustained a drop of ≥20 mm Hg systolic BP or ≥10 mm Hg diastolic BP throughout the 110 seconds stand, to represent those participants with the most severe OH (OH110). The OH110 group have a sustained drop in BP as defined by the American Autonomic Society.²³

Covariate Information

Covariate information was recorded at the computer-aided personal interview and health assessment. Information obtained included sex, age, self-reported presence of hypertension, angina, heart attack, heart failure, diabetes mellitus, stroke, transient ischemic attack, irregular heart rhythm, and heart murmur. Cardiovascular conditions were grouped into a categorical variable 0, 1, or ≥2 conditions. Medication information was obtained at the computer-aided personal interview and was coded using the Anatomical Therapeutic Chemical Classification (ATC). Medications controlled for in this study included all classes of antihypertensive medications including antihypertensive medications (ATC C02), diuretics (ATC C03), β-blockers (ATC C07), calcium channel blockers (ATC C08), and renin-angiotensin system agents (ATC C09). Antidepressant medications were also controlled for and vitamin D supplement use. The proportion of those reporting insulin treatment was also recorded. Smoking status was recorded at the computer-aided personal interview. Obesity was measured as a BMI >30 kg/m². Systolic and diastolic BP were measured at the health assessment using traditional oscillometric methods.

Statistical Analysis

All statistical analysis was performed using Stata 14 (Stata Corporation). For descriptive characteristics, groups were compared using ANOVA for continuous variables and χ^2 for categorical variables. Logistic regression was used to assess for an association between ISBP and vitamin D category. Univariate analysis was performed as well as multivariable analysis controlling for age, sex, baseline systolic BP, diastolic BP, heart rate rise, vitamin D supplement use, antidepressant medication, antihypertensive medications,

number of cardiovascular conditions, season of blood collection, smoking, and BMI. Similarly, univariate logistic regression was used to assess for an association between OH110 and vitamin D category, followed by multivariable analysis controlling for all covariates. To ensure that vitamin D supplement use did not bias the results, the analysis was repeated with the exclusion of those participants taking vitamin D supplements.

Results

A total of 8175 participants were recruited to the TILDA study. Of these, 5035 attended the health assessment and were eligible for inclusion in the study. There were 564 participants who did not have adequate active stand data for analysis, and of the remaining participants, 258 did not have measurement of 25(OH)D concentration. Therefore, the final sample for analysis was 4209 participants. Population characteristics are described in Table 1. Participants who were deficient in 25(OH)D (according to Institute of Medicine guidelines), were more likely to be smokers, more likely to take antihypertensive medications, had higher levels of cardiovascular disorders and higher mean systolic BP compared with those with sufficient status. In addition, those with deficient status were less likely to consume vitamin D supplements and had a lower BMI. Within our substudy population, 1.05% (n 44) reported insulin treatment.

Univariate logistic regression to assess an association between ISBP and vitamin D category found that, compared with a reference of sufficient, those with deficient (odds ratio [OR], 1.18; 95% CI, 0.86–1.61; $P=0.303$) or insufficient (OR, 1.13; 95% CI, 0.91–1.42; $P=0.272$) concentrations of 25(OH)D were no more likely to have evidence of ISBP on active stand. There was also no evidence of an association after controlling for age, sex, baseline systolic BP, baseline diastolic BP, vitamin D supplement use, antihypertensive medications, antidepressant medications, number of cardiovascular conditions, diabetes mellitus, season of collection of blood sample, smoking, BMI, and heart rate rise in a multivariable logistic regression (Table 2). Univariate logistic regression to assess an association between OH110 and vitamin D category found that, compared with a reference of sufficient, those with deficient (OR, 0.85; 95% CI, 0.52–1.40; $P=0.528$) or insufficient (OR, 0.85; 95% CI, 0.61–1.21; $P=0.384$) status did not have a significantly higher odds of OH110. On controlling for all confounders, there were no statistically significant associations in a multivariable logistic regression (Table 3).

The analysis was repeated removing vitamin D supplement users. Again, ISBP was not statistically more likely in participants with deficient (OR, 1.26; 95% CI, 0.92–1.74; $P=0.147$) or insufficient (OR, 1.19; 95% CI, 0.94–1.51; $P=0.132$) status.

Table 1. Population Characteristics*

Participant Characteristic	25(OH)D Categories			
	Deficient 0–30 nmol/L (n=486)	Insufficient 30–50 nmol/L (n=1220)	Sufficient ≥50nmol/L (n=2480)	P Value
25(OH)D, nmol/L	23.23±5.1	40.17±5.7	73.00±17.0	<0.001
Age, y	61.58±8.7	61.48±8.4	61.65±8.0	0.817
Female sex, % (n)	51.2 (249)	51.4 (627)	54.4 (1350)	0.144
Smoking status (base never), % (n)				
Past	39.7 (193)	39.3 (480)	39.7 (985)	
Current	23.7 (115)	18.2 (222)	11.4 (282)	<0.001
Antihypertensive medications, % (n)	35.0 (170)	36.1 (440)	30.0 (744)	<0.001
Antidepressant medications, % (n)	6.2 (30)	5.7 (70)	5.9 (145)	0.942
Vitamin D supplements, % (n)	1.7 (8)	4.8 (59)	12.5 (310)	<0.001
No. of CVD conditions, % (n)				
1	33.5 (163)	34.8 (425)	28.7 (718)	
≥2	11.9 (58)	11.4 (140)	9.4 (236)	<0.001
Diabetes mellitus, % (n)	9.47 (46)	8.1 (99)	5.0 (125)	<0.001
Mean SBP, mm Hg	135.5±20.0	135.2±19.2	133.8±19.3	0.001
Mean DBP, mm Hg	82.6±11.5	82.7±11.1	82.0±11.0	0.132
Season of collection, % (n)				
Winter and Spring	80.2 (390)	66.1 (806)	43.9 (1088)	
Summer and Autumn	19.8 (96)	33.9 (414)	56.1 (1391)	<0.001
BMI, kg/m ²	22.9±6.4	29.2±4.9	28.0±4.3	<0.001
HR rise on stand (bpm)	20.2±9.7	20.0±8.9	19.7±8.7	0.359

Groups were compared using ANOVA for continuous variables and χ^2 for categorical variables. 25(OH)D indicates serum 25-hydroxyvitamin D; BMI, body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; HR heart rate; and SBP, systolic blood pressure.

*Data are means±SD or percentage as appropriate.

Table 2. Multivariable Logistic Regression to Assess for Association Between Vitamin D Status and OH(40)

Impaired Stabilization of BP	OR	95% CI	P Value
25(OH)D category, base sufficient (≥ 50 nmol/L)			
0–30, nmol/L	1.17	0.81–1.68	0.390
30–50, nmol/L	1.16	0.90–1.49	0.243
Age, y	1.07	1.06–1.09	<0.001
Female sex	1.23	0.98–1.54	0.074
Baseline SBP, mm Hg	1.00	0.99–1.01	0.270
Baseline DBP, mm Hg	1.01	1.00–1.03	0.013
Vitamin D supplement use	0.96	0.67–1.38	0.862
Antidepressant use	1.87	1.29–2.72	0.001
Antihypertensive use	0.92	0.67–1.26	0.610
No. of CVD conditions (base none)			
1	1.40	1.03–1.91	0.029
≥ 2	1.69	1.13–2.53	0.010
Diabetes mellitus	1.04	0.68–1.58	0.832
Season of collection: Summer and Autumn	1.12	0.90–1.41	0.284
Current smoker	1.36	1.00–1.84	0.043
BMI, kg/m ²	0.95	0.92–0.97	<0.001
HR rise on stand, bpm	0.97	0.96–0.98	<0.001

25(OH)D indicates serum 25-hydroxyvitamin D; BMI, body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

Similarly, OH110 was not more likely in participants with deficient (OR, 0.93; 95% CI, 0.56–1.54; $P=0.784$) or insufficient (OR, 0.88; 95% CI, 0.61–1.27; $P=0.520$) status. Continuous 25 (OH) Vitamin D status was also assessed and predictive margins for probability of ISBP and OH110 with 95% CIs are displayed in Figures 1 and 2, respectively.

Discussion

To our knowledge, this is the largest and most comprehensive population study to investigate the relationship of vitamin D status with OH in older adults. We observed no association of vitamin D status with indicators of impaired stabilization of BP or OH after adjustment for relevant covariates. Our findings are in agreement with Veronese et al¹⁴ who, in the largest study conducted before ours ($N=2640$ older adults), also found no association. Furthermore, in a 1-year randomized controlled trial of 75 older adults (aged >70 years), high-dose vitamin D supplementation (100 000 IU) did not improve OH.¹⁵

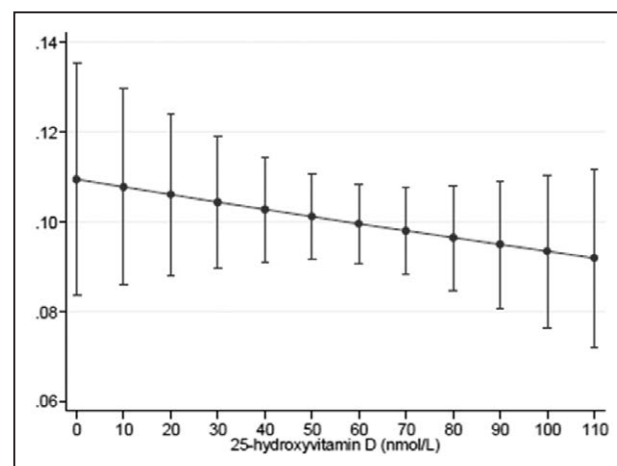
These results are in direct contrast to the majority of vitamin D-OH reported studies^{11–13,16,17,19,20} 2 of which were prospective^{16,19} that observed an increased risk of OH with vitamin D deficiency over 12 months¹⁶ and 4 years.¹⁹ However, it is possible that important nonadjusted confounders could have influenced these findings. In the Duval et al¹⁶ study, the study population was from an intervention trial where 70% of the subjects were either taking acetylcholinesterase inhibitors or memantine.²⁴ Acetylcholinesterase inhibition appears effective in the treatment of neurogenic orthostatic hypotension²⁵

Table 3. Multivariable Logistic Regression to Assess for Association Between Vitamin D Status and OH(110)

OH Sustained—110 Seconds	OR	95% CI	P Value
25(OH)D category, base sufficient (≥ 50 nmol/L)			
0–30, nmol/L	0.89	0.50–1.58	0.696
30–50, nmol/L	0.92	0.63–1.34	0.676
Age, y	1.05	1.03–1.07	<0.001
Female sex	1.31	0.93–1.85	0.117
Baseline SBP, mm Hg	1.01	1.00–1.02	0.035
Baseline DBP, mm Hg	1.00	0.98–1.02	0.653
Vitamin D supplement use	1.12	0.69–1.81	0.626
Antidepressant use	1.53	0.87–2.66	0.133
Antihypertensive use	1.10	0.69–1.76	0.671
No. of CVD conditions (base none)			
1	1.43	0.91–2.24	0.116
≥ 2	1.30	0.70–2.40	0.393
Diabetes mellitus	0.94	0.49–1.83	0.876
Season of collection: Summer and Autumn	1.23	0.88–1.70	0.211
Current smoker	1.27	0.81–1.98	0.286
BMI, kg/m ²	0.91	0.87–0.95	<0.001
HR rise	0.96	0.94–0.98	0.002

25(OH)D indicates serum 25-hydroxyvitamin D; BMI, body mass index; CVD, cardiovascular diseases; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

while it has also been associated with increasing the concentration of 25(OH)D.²⁶ In the other prospective study,¹⁹ the study population was based on the Progetto Veneto Anziani Study where there were no exclusion criteria and may have included participants who were institutionalized, severely disabled, or bedridden.²⁷ Nevertheless, these inconsistencies are minor in comparison with the larger problems within this area of research. As stated earlier, these problems include heterogeneous population groups, different vitamin D methodologies,

**Figure 1.** Predictive margins for ISBP based on 25-hydroxyvitamin D status.

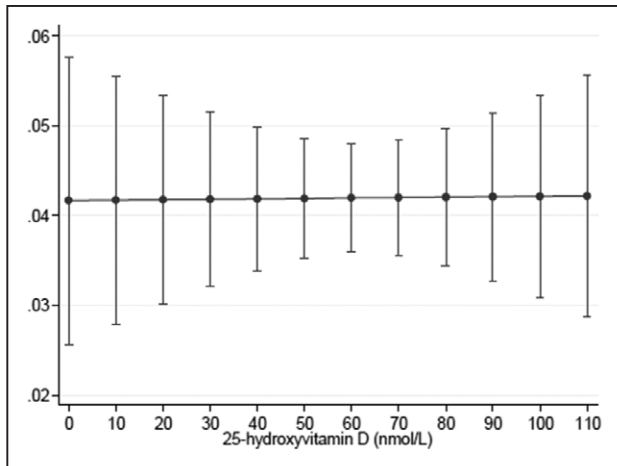


Figure 2. Predictive margins for orthostatic hypotension (OH)110 based on 25-hydroxyvitamin D status.

different 25(OH)D cutoffs, lack of study power and standardization and different BP measurement methodologies. Furthermore, a biological mechanism of effect for vitamin D and OH has yet to be proven while there is little randomized controlled trial evidence linking vitamin D with the common causes/conditions of severe OH. Thus, there is a difficulty interpreting a clinical utility from the data.

Although we, and others, observed no association between vitamin D and OH, the usefulness of vitamin D in the management and possibly the prevention of OH cannot be dismissed. For example, those with OH are more likely to fall²⁸ and thus also sustain fractures.²⁹ The strongest evidence for the health benefits for vitamin D exists for bone health and muscle function.^{7,9} Thus, checking vitamin D levels and optimizing vitamin D status for bone health and muscle function is important in this high-risk group. Furthermore, our study and all others to date in this area have found no increased risk of OH with higher concentrations of 25(OH)D or with large doses of vitamin D supplementation. Thus, the achievement of optimal vitamin D status in this patient cohort could have benefits for muscle, bone, and falls without an adverse consequence for BP. There is also the consideration of the age dimension, the hypothesis that the effects of vitamin D are long-term over decades (long-latency deficiency disease³⁰) and once OH has been established and the pathological features have set in it is too late to treat with vitamin D or to observe an association. However, there are currently no long-term longitudinal studies examining vitamin D status and OH from young adults to older age.

Our study has some important strengths. First, it is a nationally representative population study and the largest in this area to date. It also uses the gold standard method of vitamin D analysis that has international standardization along with reported assay coefficient of variation for quality control. In addition, we used recognized cutoffs to describe blood vitamin D status, and we were able to examine associations with and without vitamin D supplements. Second, we used beat-to-beat measurement of BP response to stand using a finometer, which allowed a precise assessment of BP behavior in response to orthostasis, and this can detect more subtle fluctuations in BP. Our study also has some limitations, we did not use the traditional definition of OH, our data are cross-sectional, and

the cardiovascular disorders were self-reported (though were cross-referenced with the medication data). In addition, because of the sampling criteria, our findings may not be applicable to nonwhites, older adults in institutional care or those with severe cognitive impairment.

Perspectives

From our findings in the largest study yet investigated, we conclude that there is no association with vitamin D status and OH in older adults. Using the evidence from our data and other studies in the literature, we cannot recommend that further randomized controlled trials should be undertaken until we identify the target population, agree on standardization of vitamin D methodologies and cutoffs and agree an OH outcome measure.

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Disclosures

None.

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Novelty and Significance

What Is New?

- It is a large longitudinal study using a gold standard of vitamin D measurement, standardized cutoffs and includes a large, well-described population-representative sample of older people with a diagnosis of orthostatic hypotension based on continuous beat-to-beat readings.

What Is Relevant?

- Blood vitamin D concentration is not associated with impaired stabilization of blood pressure or orthostatic hypotension in older Irish adults.
- These findings are also relevant in the context of new treatments of orthostatic hypotension and the formation of international vitamin D guidelines for vitamin D requirements based on health outcomes.

Summary

There is no association with vitamin D status and orthostatic hypotension in older adults. Using the evidence from our data and other studies in the literature, we cannot recommend that further randomized controlled trials should be undertaken until we identify the target population, agree on standardization of vitamin D methodologies and cutoffs and agree an orthostatic hypotension outcome measure.