DOI:
10.1016/j.jash.2016.06.038

Document Version
Peer reviewed version

Accepted Manuscript

Hypovitaminosis D Predicts the Onset of Orthostatic Hypotension in Older Adults

Nicola Veronese, Caterina Trevisan, Francesco Bolzetta, Marina De Rui, Sabina Zambon, Estella Musacchio, Leonardo Sartori, Brendon Stubbs, Egle Perissinotto, Gaetano Crepaldi, Enzo Manzato, Giuseppe Sergi

PII: S1933-1711(16)30404-1

DOI: 10.1016/j.jash.2016.06.038

Reference: JASH 937

To appear in: *Journal of the American Society of Hypertension*

Received Date: 8 May 2016

Revised Date: 5 June 2016

Accepted Date: 21 June 2016

Please cite this article as: Veronese N, Trevisan C, Bolzetta F, De Rui M, Zambon S, Musacchio E, Sartori L, Stubbs B, Perissinotto E, Crepaldi G, Manzato E, Sergi G, Hypovitaminosis D Predicts the Onset of Orthostatic Hypotension in Older Adults, *Journal of the American Society of Hypertension* (2016), doi: 10.1016/j.jash.2016.06.038.

HYPOVITAMINOSIS D PREDICTS THE ONSET OF ORTHOSTATIC HYPOTENSION IN OLDER ADULTS

Short title: Vitamin D and orthostatic hypotension in the elderly

Nicola Veronese[a], Caterina Trevisan[a], Francesco Bolzetta[a], Marina De Rui[a], Sabina Zambon[b,c], Estella Musacchio[c], Leonardo Sartori[c], Brendon Stubbs[d,e], Egle Perissinotto[f], Gaetano Crepaldi[b], Enzo Manzato[a,b], Giuseppe Sergi[a]

[a] Department of Medicine (DIMED), Geriatrics Division; University of Padova, Italy.

[b] National Research Council, Neuroscience Institute, Padova, Italy.

[c] Department of Medicine DIMED, Clinica Medica I, University of Padova, Italy.

[d] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom.

[e] Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London Box SE5 8 AF, United Kingdom

[f] Department of Cardiac, Thoracic and Vascular Sciences - Biostatistics, Epidemiology and Public Health Unit, University of Padova, Padova, Italy.

Correspondence to:

Nicola Veronese, University of Padova, Department of Medicine - DIMED, Geriatrics Division, Via Giustiniani 2, 35128 Padova, Italy. Phone: +390498218492; Fax: +390498211218. Email: ilmannato@tiscali.it; ilmannato@gmail.com

Funding source: The data collection phase of the PRO.V.A. study was supported by the Fondazione Cassa di Risparmio di Padova e Rovigo; University of Padova; the Azienda Unità Locale Socio Sanitaria 15 and 18 of the Veneto Region; and a grant from the Veneto Regional Authority (Ricerca Sanitaria Finalizzata n.156/03). The data analysis phase was also financed by a grant of the University of Padova (Population aging - economics, health, retirement and the welfare state - POPA_EHR).

Conflict of interest: none.

ABSTRACT

A number of small cross sectional studies have demonstrated that hypovitaminosis D (represented by low 25 hydroxyvitamin D (25OHD) levels) is associated with orthostatic hypotension (OH). We investigated if hypovitaminosis D is associated with the onset of OH in older adults over a follow-up of 4.4 years. 25OHD was categorized using sex specific quartiles; OH was defined as a drop of ≤20 mm Hg in systolic or ≤10 mm Hg in diastolic blood pressure <3 minutes of standing. Among 1,308 elderly without OH at baseline, using an adjusted logistic regression analysis and taking those with higher baseline serum 25OHD as reference, there was a significant increase in the onset of OH in those with lower serum 25OHD levels. The association was significant only in women when we stratified by sex. In conclusion, hypovitaminosis D predicts the onset of OH in older adults, particularly in women.

Keywords: vitamin D; orthostatic hypotension; aged.

INTRODUCTION

Orthostatic hypotension (OH) is a common condition in the elderly. Its prevalence significantly varies with age reaching approximately 30% in those aged 70 years and over.[1] OH is traditionally related to a greater risk of falls, traumas, and fractures.[1] However, recent research has proposed OH as a potential cardiovascular risk factor, since OH seems to be able to predict cardiovascular events and all-cause mortality.[2–5]

A number of studies have demonstrated a possible role for hypovitaminosis D, defined as lower serum 25-hydroxyvitamin D (25OHD) levels, as a potential risk factor for vascular diseases, including hypertension. The association between 25OHD and hypertension was recently reported in a large meta-analysis, showing that increased 25OHDconcentrations were significantly associated with decreased odds of hypertension.[6] Vitamin D receptors are present in endothelial cells and may have a crucial role in the modulation of vessels in animal models.[7] Therefore, it appears possible that vitamin D could play a role in modulating vascular response during orthostatism.

However, data about the role of hypovitaminosis D as a possible risk factor for OH in humans is predominantly limited to cross-sectional studies.[8–13] Altogether, these studies showed a significant association between hypovitaminosis D and OH [8–11], although the number and type of adjustments seems to be an important factor.[12] To the best of our knowledge, only one study has prospectively assessed the association between hypovitaminosis D and OH.[14] The authors found that hypovitaminosis D predicts the onset of OH at follow-up, but had various limitations, in particular the small sample size (n=51) and the short follow-up (1 year) which limits the conclusions of these findings.[14]

We therefore aimed to investigate the association between hypovitaminosis D and the onset of OH in a large representative cohort of older men and women over a mean follow-up of 4.4 years. We hypothesized that low serum 25OHD would predict the onset of OH at the follow-up.

METHODS

Data source and subjects

This work is based on data of the *Progetto Veneto Anziani* (Pro.V.A.) study, an observational cohort study of all community-dwelling subjects aged ≥65 residing in Camposampiero and Rovigo (two towns in northern Italy surrounded by rural and industrial areas) without using any specific exclusion criteria.[15] The baseline visit was made between October 1995 and November 1997.
The follow-up evaluation was scheduled to occur at 4 years after baseline. The follow-up period was in mean 4.4, censoring the data after 6 years from baseline evaluation.
The local ethical committees of Padova University and the Local Health Units (USSL) n. 15 and n. 18 of the Veneto Region approved the study protocol, and participants gave their written informed consent.

Clinical data

Participants were examined at city hospitals by trained physicians and nurses. Regular physical activity was defined as ≥4 h/week (i.e., the upper half of the median split of the entire sample) in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing, or physical exercise). Smoking status was classified as “current” vs. “former (for at least 1 year in the past)/never”. Heavy alcohol drinkers were defined using the criteria suggested by the National Institute of Alcohol Abuse and Alcoholism, i.e., more than 15 drinks weekly for men and 8 for women.[16] Living alone was categorized as “yes” vs. “no”.
We collected the following anthropometric parameters: height (measured or estimated from knee-height, when this proxy indicator was more accurate), weight, body mass index (BMI; in kg/m^2).
Functional status and social independence were assessed using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL).[17,18] Cognitive function was assessed using 30 items mini-mental state examination (MMSE).[19]

Participants' clinical status and comorbidities were evaluated by board-certified physicians through standardized questionnaires considering anamnestic data, self-reported symptoms, medical and hospital records, and results from blood tests and physical examination. For the purpose of our study, the following diseases were assessed: history of hypoacusis, hypovisus, diabetes mellitus, cardiovascular diseases (CVD), hip fracture and osteoarthritis, and hypertension.[15] Diabetes was defined as fasting plasma glucose levels ≥7.0 nmol/L, HbA1c ≥6.5%, the use of glucose-lowering drugs, or a history of a 2h post-load glucose ≥11.1 nmol/L.[20] As CVD we considered the presence of one of the following: congestive heart failure; angina requiring a stent, angioplasty or hospitalization; myocardial infarction; and stroke. Hypertension was defined as the presence of systolic BP ≥140 mm Hg, diastolic BP≥90 mm Hg, or current use of antihypertensive medications.[21] Both at the baseline and at the follow-up, the physician performing the physical examination diagnosed any disease using all the previously-listed measures. A specialist in the field (e.g. a cardiologist for CVD) confirmed any disease presence using a standardized algorithm considering all the medical information collected on each participant.

Laboratory tests

A venous blood sample was obtained after an overnight fast for biochemical tests, which were performed at the central laboratory of Padova hospital using standard and quality-controlled procedures. Renal function was assessed using the estimated glomerular filtration rate (eGFR) with the Modified Diet in Renal Disease formula. Serum intact parathormone (PTH) levels were measured using a 2-site immunoradiometric assay (N-tact PTHSP; DiaSorin): the intra-assay and interassay coefficients of variation (CVs) for parathormone were 3.0% and 5.5%, respectively. Season of blood collection was defined as winter, spring, summer, or autumn.

Definition of risk categories

Serum 25OHD levels were measured by radioimmunoassay (RIA kit; DiaSorin). The intra-assay and inter-assay CVs for 25OHD were 8.1% and 10.2%, respectively. In this work, we divided the sample using gender-specific quartiles, taking as cut-offs for men 69, 101 and 142 nmol/L and for women 42, 64, and 92 nmol/L, respectively.

Definition of outcome (orthostatic hypotension)

Every blood pressure measurement was taken by a trained nurse. The cuff was chosen based on this circumference among little (<24 cm), normal (24–32 cm), and big (33–41 cm) size. Clinostatic blood pressure was measured in both arms 3 times with 30-second intervals between them with a mercury sphygmomanometer (Erkameter 300). Participants were in the lying position, and the mean value was taken for reference. Orthostatic blood pressure was then measured after 1 and 3 minutes of standing. According to the guidelines of the consensus committee of the American Autonomic Society and the American Academy of Neurology, orthostatic hypotension was defined as a drop of ≤20 mm Hg in systolic blood pressure, or ≤10 mm Hg in diastolic blood pressure within 3 minutes of standing up.[22]

Statistical analyses

To generalize the Pro.V.A. sample to the population at large in the two geographical areas considered, a set of weights was defined according to the sex and age distribution of the reference population (1991 Census, Italy), and to the sample fraction. For continuous variables, normal distributions were tested using the Shapiro-Wilk test. Participants' characteristics were summarized using means (± standard deviations, SD) for continuous variables, and percentages for categorical variables among baseline serum 25OHD quartiles. Age and gender adjusted *p*-values were calculated for continuous variables using a general linear model (GLM) applying the Bonferroni's correction, while for categorical variables logistic regression was applied.

The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time. However, since this test showed a $p<0.0001$, a logistic regression analysis instead of Cox's proportional hazard models was used to assess the associations between baseline 25OHD levels and incident OH. Factors known to be associated with 25OHD and/or OH were considered for inclusion in the analysis. The covariates included in the final model were: i) statistically significantly different ($p<0.05$) between participants having <50, 50-74 and ≥75 nmol/L at the multivariable; ii) having a p-value<0.10 in the respective univariable analyses. Collinearity among covariates was estimated with the variance inflation factor (VIF) using a value of ≥2 as an exclusion criterion. Although serum PTH levels were collinear with 25OHD (VIF=5.82), we included this parameter since it seems that high PTH levels play a role in the pathogenesis of CVD.[23]

In our primary analyses, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare the onset of new cases of OH, using baseline 25OHD quartiles as the key independent explanatory variable in the sample as whole and according to gender. P values for trend were calculated using the Wald test based on a score with the median value of each serum 25OHD group. All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was set at p-value ≤0.05. We used Bonferroni-correction (with alpha=0.05/3, i.e., p=0.017).

RESULTS

Flow-chart of study flow

Figure 1 shows the flowchart of study participants used within our analysis.. By comparison with the sample completing the follow-up, those who dropped out were significantly older, more frequently men, and they had significantly lower serum 25OHD levels and OH at the baseline ($p<0.0001$ for all comparisons).

Baseline characteristics

The sample consisted of 1308 community-dwelling elderly subjects. The mean age of the sample was 70.0±5.8 [range: 65-93] years, 59.7% were women. The mean baseline 25OHD was significantly higher in men than in women (114.1±61.1 vs. 72.8±41.4 nmol/L; $p<0.0001$).

Table 1 shows the characteristics of the sample according to baseline serum 25OHD values. Those with hypovitaminosis D (<69 nmol/L in men and <42 nmol/L in women) were significantly older than other groups ($p<0.0001$). After adjusting for age and sex, they were more obese, less previous smokers and heavy alcohol drinkers, more sedentary and disabled than those with higher 25OHD levels (**Table 1**).

Regarding medical conditions, the participants with hypovitaminosis D showed a significant higher presence of comorbidities (except for diabetes), worse renal function and they took a higher number of drugs, including anti-hypertensives, than other participants (**Table 1**).

Finally, participants with hypovitaminosis D made the blood collection more frequently in winter/autumn than other participants (**Table 1**).

Follow-up analyses

During follow-up period, we identified 463 (111 with a significant fall in BP at the 1st minute and 220 at both 1st and 3rd minutes) new cases of OH (201 M and 262 F) with a global incidence rate of

77 (95%CI: 55-89) per 1000 persons-year. Those with OH at the follow-up had significant lower serum 25OHD concentrations than those without (91.0±55.0 vs. 86.5±52.3 nmol/L, p<0.0001).

As shown in **Table 2,** there was a significant trend in incidence of new cases of OH (Q1: 85; 95%CI: 78-89 vs. Q4: 70; 95%CI: 55-82 persons per years/1000).

Using a logistic regression analysis and taking those with baseline serum 25OHD grouped in Q4 as reference, after adjusting for potential confounders, there was a significant increase in the onset of OH in Q2 (OR=1.17; 95%CI: 1.05-1.30, p=0.02) and in Q1 (OR=1.18; 95%CI: 1.06-1.31, p=0.001) (p for trend=0.01).

In men, the association between baseline 25OHD and the onset of OH was not significant (p for trend=0.35), while in women this association was significant (Q3: OR=1.32, 95%CI: 1.15-1.52, p<0.0001; Q2: OR=1.39, 95%CI: 1.21-1.60, p<0.0001; Q1: OR=1.36, 95%CI: 1.17-1.58, p<0.0001) (p for trend<0.0001) (**Table 2**).

DISCUSSION

The current prospective cohort study found a significant association between low baseline 25OHD concentrations and the onset of new orthostatic hypotension events over 4.4 years of follow-up in a representative cohort of older men and women. This relationship seems to be significant only in women. Our results shed new light on the longitudinal relationship between low 25OHD and OH and is to our knowledge the first representative large scale cohort study considering this important question.

In vitro and animal research has proposed several explanations for the association between 25OHD and OH. First, vitamin D could be important for the proliferation and growth of cultured vascular smooth muscle cells necessary for a good compliance of the arteries.[24] Ni et al. have demonstrated in an animal model that the elimination of the vitamin D receptor from endothelial cells corresponded to a reduced arterial compliance.[7] Moreover, it seems that the active form of vitamin D could activate p38 mitogen-activated protein kinase and phosphatidylinositol kinase[24], which induces oxidative stress and consequently a structural disintegration and stiffening of the arterial wall.[25] Altogether these findings suggest that low vitamin D levels could play a role in reducing compliance in arteries making difficult the adaptation during standing up. Second, some research have shown that hypovitaminosis D could be associated with a dysfunction of the baroreflex neural arc (i.e. there is loss of buffering ability, and wide excursions of pressure and heart rate) leading to an inappropriate adaptive response to standing up.[26] Vitamin D metabolites regulate the genetic expression of neurotrophins (nerve growth factor and neurotransmitters) with a consequent reduction in appropriate compensatory mechanisms during standing up.[27,28] Third, another explanation relies on the fact that hypovitaminosis D could be involved in increasing blood pressure levels which may result in the prescription of antihypertensive drugs and consequent greater risk of iatrogenic OH.[29] In agreement with this hypothesis, within our study, those with hypovitaminosis D at the baseline had a higher presence of hypertension and more frequently used anti-hypertensive

medications. However, the use of anti-hypertensive medications and hypertension were used as covariates in our analyses, not altering the significance of the association and making this assumption less reliable.

Another possible explanation is that the group of participants with the highest 25OHD values (and lowest incidence of OH at follow-up) had lower BMI, higher physical activity and lower frequency of antihypertensive drugs usage compared to the other 25OHD categories, suggesting that the participants with higher 25OHD concentrations are healthier and so less prone to the onset of OH. Activation of the muscle venous pump of the legs is more effective in leaner than obese people and it could be considered as a 'second heart' capable of translocating blood against a substantial pressure gradient with a consequent less presence of OH. [30]

Considering the literature in human studies, very few authors have reported an association between hypovitaminosis D and OH.[8–12] Altogether these studies suggested that participants with OH had significantly lower serum 25OHD levels and that after the correction for potential confounders the association remain significant, although the number and kind of covariates included seem to be important to explain this association.[12] Whilst helpful, the cross-sectional design prevents any consideration of the directionality of this observed relationship. Indeed reverse causation is also possible, i.e. that OH causes limitation in physical movement, loss of independence with subsequent reduced sun exposure and hypovitaminosis D as a result. We attempted to address concerns regarding the directionality of the relationship and reverse causality by conducting a longitudinal study in which those with pre-existing OH were excluded. To the best of our knowledge, only one previous longitudinal study reported that hypovitaminosis D at the baseline predicts the onset of OH at follow-up in 51 participants followed for one year being in agreement with our findings.[14] Clearly, the lack of generalizability and short duration of follow up preclude any meaningful conclusion from this study. On the contrary, one RCT has demonstrated no improvement in OH after oral vitamin D supplementation.[31] Despite its limitations, the findings of this trial resulted in

agreement with a recent large meta-analysis about the lack of effects of vitamin D supplementation on blood pressure[32], strengthening the need for more research about how to properly improve vitamin D status in humans [33] and that probably larger high quality RCTs are needed for advising or not the use of vitamin D supplementation in people affected by OH.

Our results were more evident in women than in men, suggesting important gender differences that are also present considering the mean 25OHD levels. Although, the precise reason of this difference is not known, we could hypothesize that OH was less diagnosed in women than in men according, with the findings of a large meta-analysis showing that women had a greater cardiovascular risk than men.[34] These differences may be explained by potential differences in diagnosis of CVD and cardiovascular risk factors, including OH. In several Western countries, in fact, men with at higher risk of CVD were diagnosed earlier than women.[35] Therefore, it is possible that also women with hypovitaminosis D at the baseline were less followed-up than men increasing the risk of OH during follow-up. Another explanation could be a lack of power of our analysis for men, since these analyses included about a third of the total women. Due the preliminary nature of our findings, future representative longitudinal studies are needed for clarifying these differences.

Whilst the study has numerous strengths, the findings of this study should be interpreted within its limitations. The first is that we did not assess 25OHD concentrations at the follow-up, being not able to account for the inherent changes of this marker. Although literature suggests that serum 25OHD did not change between evaluations[36], a possible bias should be taken in account. Second, a possible selection bias could be possible since only 1,308 participants among the 3,099 initially included in the PRO.V.A. study were included in this survey. However, since 30% were excluded having a diagnosis of OH at the baseline, our findings showed how frequent is this condition. This is indirectly confirmed by our longitudinal findings showing that almost 40% of the participants initially included had a diagnosis of OH during follow-up period. In this scenario, it should be noted

that a consistent part (about 25% of the participants having OH at follow-up) reported this condition for a fall in BP at 1st minute only, indicating a less severe disease than other participants having OH. A third limitation lies in that we only measured orthostatic hemodynamic parameters at 1 and 3 minutes, whereas many cases of orthostatic hypotension in people aged >65 years are known to develop later on.[37,38] Finally, another limitation could be considered the relatively short follow-up period of observation.

In conclusion, hypovitaminosis D predicts the onset of orthostatic hypotension, independently of potential confounders, in a large representative cohort of older men and women. Well-designed trials including an adequate proportion of older subjects are mandatory to confirm our findings.

REFERENCES

1. Gupta V, Lipsitz LA. Orthostatic Hypotension in the Elderly: Diagnosis and Treatment. Am J Med [Internet] 2007 [cited 2015 Oct 4];120:841–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17904451

2. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis, and Treatment. J Am Coll Cardiol [Internet] 2015 [cited 2015 Sep 1];66:848–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26271068

3. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J [Internet] 2015 [cited 2015 Jul 1];36:1609–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25852216

4. Xin W, Lin Z, Mi S. Orthostatic hypotension and mortality risk: a meta-analysis of cohort studies. Heart [Internet] 2013 [cited 2015 Oct 4];100:406–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23878177

5. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J Hypertens [Internet] 2014 [cited 2015 Oct 4];32:1562–71; discussion 1571. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24879490

6. Vimaleswaran KS, Cavadino A, Berry DJ, Jorde R, Dieffenbach AK, Lu C, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. lancet Diabetes Endocrinol [Internet] 2014 [cited 2015 Feb 2];2:719–29. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4582411&tool=pmcentrez&rend

ertype=abstract

7. Ni W, Watts SW, Ng M, Chen S, Glenn DJ, Gardner DG. Elimination of vitamin D receptor in vascular endothelial cells alters vascular function. Hypertension [Internet] 2014 [cited 2015 Aug 31];64:1290–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25201890

8. Annweiler C, Schott a.-M, Rolland Y, Beauchet O. Vitamin D deficiency is associated with orthostatic hypotension in oldest-old women. J Intern Med [Internet] 2014;276:285–95. Available from: http://doi.wiley.com/10.1111/joim.12201

9. Jang W, Park J, Kim JS, Youn J, Oh E, Kwon KY, et al. Vitamin D deficiency in Parkinson's disease patients with orthostatic hypotension. Acta Neurol Scand [Internet] 2015;132:242–50. Available from: http://doi.wiley.com/10.1111/ane.12390

10. Soysal P, Yay A, Isik AT. Does vitamin D deficiency increase orthostatic hypotension risk in the elderly patients? Arch Gerontol Geriatr [Internet] 2014;59:74–7. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0167494314000387

11. McCarroll KG, Robinson DJ, Coughlan a., Healy M, Kenny R a., Cunningham C. Vitamin D and orthostatic hypotension. Age Ageing [Internet] 2012;41:810–3. Available from: http://www.ageing.oxfordjournals.org/cgi/doi/10.1093/ageing/afs088

12. Veronese N, Bolzetta F, De Rui M, Zambon S, Corti MCM-C, Musacchio E, et al. Serum 25-Hydroxyvitamin D and Orthostatic Hypotension in Old People: The Pro.V.A. Study. Hypertension [Internet] 2014;64:481–6. Available from: http://hyper.ahajournals.org/cgi/doi/10.1161/HYPERTENSIONAHA.114.03143

13. Ometto F, Stubbs B, Annweiler C, Duval GT, Jang W, Kim H-T, et al. Hypovitaminosis D and orthostatic hypotension: a systematic review and meta-analysis. J Hypertens [Internet] 2016 [cited 2016 Apr 11];Available from: http://www.ncbi.nlm.nih.gov/pubmed/27027426

14. Duval GT, Brangier A, Barré J, Launay CP, Beauchet O, Annweiler C. Vitamin D

Deficiency and Incident Onset of Orthostatic Hypotension in Older Adults: Preliminary Results from the “MERE” Study. J Am Geriatr Soc [Internet] 2015 [cited 2015 Aug 20];63:1245–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26096400

15. Corti M-C, Guralnik JM, Sartori L, Baggio G, Manzato E, Pezzotti P, et al. The effect of cardiovascular and osteoarticular diseases on disability in older Italian men and women: rationale, design, and sample characteristics of the Progetto Veneto Anziani (PRO.V.A.) study. J Am Geriatr Soc [Internet] 2002 [cited 2015 Nov 3];50:1535–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12383151

16. National Institute on Alcohol Abuse and Alcoholism. NIAAA Council Approves Definition of Binge Drinking. NIAAA Newsl [Internet] 2004;3:3. Available from: http://pubs.niaaa.nih.gov/publications/Newsletter/winter2004/Newsletter_Number3.pdf

17. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist [Internet] 1969 [cited 2014 Dec 8];9:179–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5349366

18. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist [Internet] 1970 [cited 2015 Jul 20];10:20–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/5420677

19. MF F, LN R, JE H. THe mini-mental state examination. Arch Gen Psychiatry [Internet] 1983;40:812. Available from: http://dx.doi.org/10.1001/archpsyc.1983.01790060110016

20. Association AD. 2. Classification and Diagnosis of Diabetes. Diabetes Care [Internet] 2014 [cited 2014 Dec 25];38:S8–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25537714

21. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure

measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Cou. Hypertension [Internet] 2005 [cited 2015 Mar 20];45:142–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15611362

22. American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology [Internet] 1996 [cited 2015 Sep 8];46:1470. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8628505

23. Folsom AR, Alonso A, Misialek JR, Michos ED, Selvin E, Eckfeldt JH, et al. Parathyroid hormone concentration and risk of cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J [Internet] 2014 [cited 2015 Nov 10];168:296–302. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4150218&tool=pmcentrez&rendertype=abstract

24. Yamamoto T, Kozawa O, Tanabe K, Akamatsu S, Matsuno H, Dohi S, et al. 1,25-Dihydroxyvitamin D3 Stimulates Vascular Endothelial Growth Factor Release in Aortic Smooth Muscle Cells: Role of p38 Mitogen-Activated Protein Kinase. Arch Biochem Biophys [Internet] 2002 [cited 2015 Oct 4];398:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11811942

25. Jang W, Park H-H, Lee K-Y, Lee YJ, Kim H-T, Koh S-H. 1,25-dyhydroxyvitamin D3 attenuates L-DOPA-induced neurotoxicity in neural stem cells. Mol Neurobiol [Internet] 2015 [cited 2015 Oct 7];51:558–70. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84939871929&partnerID=tZOtx3y1

26. Annweiler C, Schott A-M, Berrut G, Chauviré V, Le Gall D, Inzitari M, et al. Vitamin D and ageing: neurological issues. Neuropsychobiology [Internet] 2010;62:139–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20628264

27. Kalueff A V, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr Metab Care [Internet] 2007 [cited 2015 Oct 4];10:12–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17143049

28. Fedorowski A, Burri P, Melander O. Orthostatic hypotension in genetically related hypertensive and normotensive individuals. J Hypertens 2009;27:976–82.

29. Chen S, Sun Y, Agrawal DK. Vitamin D deficiency and essential hypertension. J Am Soc Hypertens [Internet] 2015 [cited 2015 Oct 4];Available from: http://www.ncbi.nlm.nih.gov/pubmed/26419755

30. Wieling W, van Dijk N, Thijs RD, de Lange FJ, Krediet CTP, Halliwill JR. Physical countermeasures to increase orthostatic tolerance. J Intern Med 2015;277:69–82.

31. Witham MD, Price RJG, Struthers AD, Donnan PT, Messow M, McConnachie A, et al. Effect of vitamin D supplementation on orthostatic hypotension. J Hypertens [Internet] 2014;32:1693–9. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00004872-201408000-00021

32. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, et al. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. JAMA Intern Med [Internet] 2015 [cited 2015 Aug 31];175:745–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25775274

33. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. lancet Diabetes Endocrinol [Internet] 2014 [cited 2015 May 29];2:76–89. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/24622671

34. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet (London, England) [Internet] 2014 [cited 2015 Sep 7];383:1973–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24613026

35. Krämer HU, Raum E, Rüter G, Schöttker B, Rothenbacher D, Rosemann T, et al. Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes: results from the DIANA study. Cardiovasc Diabetol [Internet] 2012 [cited 2015 Oct 9];11:88. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3526520&tool=pmcentrez&rendertype=abstract

36. Veronese N, Sergi G, De Rui M, Bolzetta F, Toffanello ED, Zambon S, et al. Serum 25-Hydroxyvitamin D and Incidence of Diabetes in Elderly People: the Pro.V.a Study. J Clin Endocrinol Metab [Internet] 2014 [cited 2015 Nov 10];99:2351–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24731010

37. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. Lancet Neurol [Internet] 2008 [cited 2015 Nov 10];7:451–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2628163&tool=pmcentrez&rendertype=abstract

38. Gibbons CH, Freeman R. Delayed orthostatic hypotension: A frequent cause of orthostatic intolerance. Neurology 2006;67:28–32.

FIGURE LEGENDS

Figure 1. Flow chart of the PRO.V.A. study

Table 1. Baseline characteristics of the 1308 subjects included in the sample

Variable	25OHD levels				*p per trend value*[*]
	Q1 ≤**69 nmol/L (M)** ≤**42 nmol/L (F)**	**Q2** **70-101 nmol/L (M)** **43-64 nmol/L (F)**	**Q3** **102-142 nmol/L (M)** **65-92 nmol/L (F)**	**Q4** **>142 nmol/L (M)** **> 92 nmol/L (F)**	
Age (years)	73.8 (6.5)	72.4 (5.7)	71.4 (5.3)	70.8 (5.1)	<0.0001[†]
Sex (females, %)	60.3	58.4	58.8	61.4	0.58 [†]
Anthropometric and demographic data					
BMI (kg/m^2)	28.3 (4.5)	28.0 (5.0)	28.0 (4.4)	27.9 (4.1)	0.004
Current smokers (%)	10.4	10.7	10.2	9.3	0.24
Former smokers (%)	28.8	31.8	33.2	32.0	0.001
Heavy drinkers (%)	10.5	13.0	18.3	15.2	<0.0001
Physical activity (≥ 4 h/week,%)	23.3	27.9	28.2	30.2	<0.0001
Living alone (%)	21.1	13.8	17.0	17.8	<0.0001
ADL score	5.4 (1.0)	5.5 (0.9)	5.6 (0.8)	5.6 (0.7)	<0.0001
IADL score	6.4 (1.6)	6.8 (1.4)	7.0 (1.3)	7.0 (1.1)	<0.0001
MMSE score	25.2 (4.4)	25.1 (3.7)	25.7 (3.8)	25.6 (3.6)	<0.0001
Medical conditions					
Diabetes (%)	13.8	13.4	13.3	15.5	0.02
Hypertension (%)	70.0	75.1	68.2	70.7	<0.0001
CVD (%)	17.4	15.8	12.1	14.8	<0.0001

Hypovisus (%)	38.7	31.9	31.6	26.2	<0.0001
Hypoacusis (%)	67.7	64.2	69.7	67.1	<0.0001
Hip fractures (%)	3.0	1.9	2.9	1.9	<0.0001
Hip osteoarthritis (%)	22.9	25.3	23.2	19.3	<0.0001
Number of medicaments	3.6 (1.8)	3.4 (1.7)	3.4 (1.7)	3.3 (1.7)	<0.0001
Use of vitamin D supplements (%)	1.9	0.8	1.1	0.8	<0.0001
Use of calcium supplements (%)	2.9	2.2	2.2	1.5	0.001
Use of antidepressive drugs (%)	4.4	4.8	6.3	2.2	<0.0001
Use of ACE inhibitors (%)	26.8	24.6	22.7	21.4	<0.0001
Use of diuretics (%)	32.3	30.5	27.0	24.4	<0.0001
Use of β-Blockers (%)	4.6	5.5	5.5	6.7	0.07
Use of Calcium channel blockers (%)	17.2	18.2	17.2	15.7	0.003
Use of central anti-hypertensives (%)	3.1	3.1	3.7	2.4	0.02
Use of vasodilators (%)	7.7	6.5	7.1	6.6	0.08
Use of nitrates (%)	6.5	5.5	4.9	2.1	<0.0001
Use of anti-hypertensive drugs (%)	71.0	70.1	66.3	68.6	<0.0001
Biochemical measures (serum)					
25(OH)D levels (nmol/l)	36.6 (16.0)	66.6 (17.8)	94.3 (23.1)	151.8 (56.1)	<0.0001
PTH (ng/l)	43.7 (29.1)	39.5 (18.4)	34.5 (16.2)	33.3 (28.1)	<0.0001
eGFR (ml/min)	72.2 (21.0)	73.9 (18.2)	71.9 (17.5)	76.5 (17.8)	<0.0001
Winter (%)	25.7	26.1	23.5	37.3	<0.0001
Spring (%)	30.4	23.8	20.3	19.2	
Summer (%)	9.6	12.3	12.8	4.1	

Autumn (%)	34.2	37.7	43.5	39.4

[*] Unless otherwise specified, p values are adjusted for age and gender using a general linear model or logistic regression, as appropriate.

[†] Not adjusted for age or gender, respectively.

Numbers are mean values (±standard deviations) or number and percentages (%), as appropriate.

Abbreviations: BMI: body mass index; ADL: activities of daily living; IADL: instrumental activities of daily living; 25OHD: 25-hydroxivitamin D; PTH: parathormone; CVD: cardiovascular diseases; eGFR: estimated glomerular filtration rate.

Table 2. Associations between serum 25-hydroxyvitamin D concentrations (categorized in sex specific quartiles) and incident orthostatic hypotension in 1308 participants of the PRO.V.A. study.

	Q4 >142 nmol/L (M) > 92 nmol/L (F)	Q3 102-142 nmol/L (M) 65-92 nmol/L (F)	Q2 70-101 nmol/L (M) 43-64 nmol/L (F)	Q1 ≤69 nmol/L (M) ≤42 nmol/L (F)	*p* for trend
Incidence parameters		***All sample (n=1308)***			
Number of cases	112	114	114	123	-
Total number	330	334	318	326	-
Incidence rate (/1000 persons year) (95%CI)	70 (55-82)	70 (66-74)	79 (77-80)	85 (78-89)	<0.0001*
Odds ratio					
Unadjusted	1	1.10 (1.00-1.21)	1.28 (1.16-1.41)	1.37 (1.24-1.50)	<0.0001
Age- and sex-adjusted model	1	1.18 (1.07-1.29)	1.23 (1.12-1.36)	1.28 (1.16-1.41)	<0.0001
Fully-adjusted model†	1	1.09 (0.99-1.21)	1.17 (1.05-1.30)	1.18 (1.06-1.31)	0.01
Incidence parameters		***Men (n=522)***			
Number of cases	51	45	50	55	-
Total number	132	129	131	130	-
Incidence rate (/1000 persons year) (95%CI)	81 (80-82)	73 (72-74)	80 (79-81)	88 (86-89)	0.01*
Odds ratio					
Unadjusted	1	0.89 (0.77-1.03)	1.06 (0.92-1.23)	1.14 (0.98-1.32)	0.01
Age- and sex-adjusted model	1	0.89 (0.77-1.03)	1.04 (0.90-1.20)	1.08 (0.93-1.26)	0.08

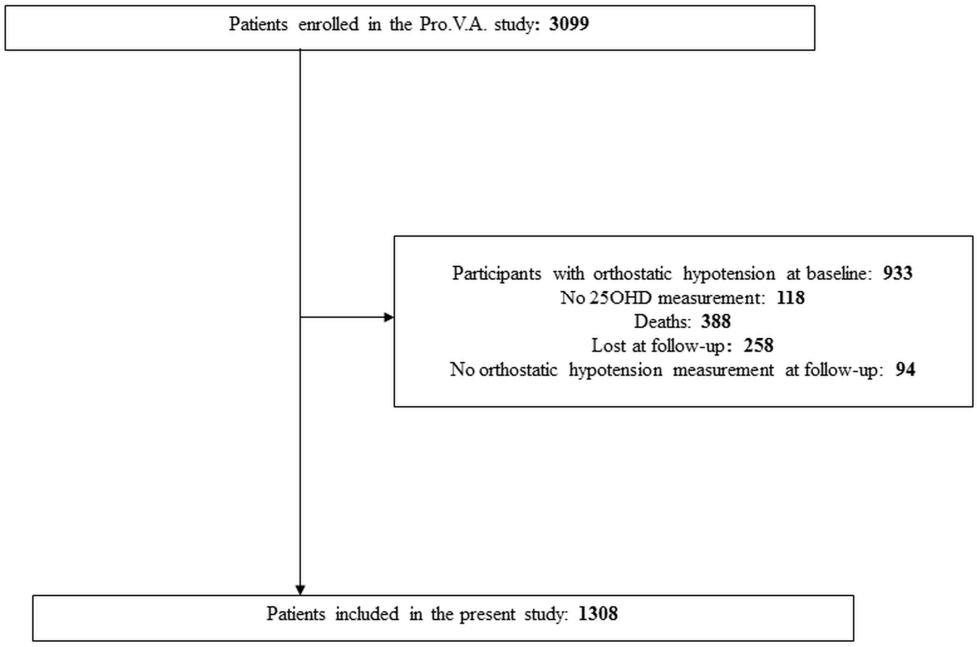
Fully-adjusted model[†]	1	0.90 (0.76-1.06)	1.02 (0.86-1.20)	1.04 (0.87-1.23)	0.35
Incidence parameters			**Women (n=786)**		
Number of cases	56	62	71	73	-
Total number	200	197	194	195	-
Incidence rate (/1000 persons year) (95%CI)	64 (55-74)	66 (65-67)	78 (77-80)	78 (77-79)	<0.0001[*]
Odds ratio					
Unadjusted	1	1.27 (1.12-1.44)	1.45 (1.28-1.64)	1.55 (1.37-1.76)	<0.0001
Age- and sex-adjusted model	1	1.26 (1.11-1.43)	1.42 (1.25-1.61)	1.50 (1.31-1.70)	<0.0001
Fully-adjusted model[†]	1	1.32 (1.15-1.52)	1.39 (1.21-1.60)	1.36 (1.17-1.58)	<0.0001

Notes:

[*]Adjusted for age.

Unless otherwise specified, data are presented as odds ratios and 95% confidence intervals.

[†] Fully-adjusted model: age, body mass index, activities of daily living, instrumental activities of daily living, Mini-Mental State Examination score, number of medications, serum levels of parathormone, creatinine, bone alkaline phosphatases (all as continuous variables); sex (males vs. females); physical activity level (≥ 4 vs. < 4 h/week); smoking habits (current vs. never/former); baseline heavy alcohol drinking, diabetes, hypertension, cardiovascular diseases, hip fracture and osteoarthritis, hypovisus, hypoacusis, use of anti-hypertension drugs, vitamin D supplementation, calcium supplementation (all as yes vs. no); hypertension at follow-up (yes/no); season of blood collection at the baseline (winter, autumn, spring and summer).



- Several cross sectional studies demonstrated that hypovitaminosis D is associated with OH.
- Our longitudinal study confirms that hypovitaminosis D could be considered as risk factor for OH.
- The association was significant only in women.