Original Article

Serum 25-Hydroxyvitamin D and the Incidence of Peripheral Artery Disease in the Elderly: The Pro.V.A Study

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Aim: This study was conducted to examine whether low serum levels of 25-hydroxyvitamin D (25OHD) are associated with a higher risk of incident peripheral artery disease (PAD) in a representative group of elderly people.

Methods: We followed 1568 community-dwelling elderly participants without PAD at the baseline (among a sample of 2097 initially eligible) over a mean of 4.4 years as part of the Progetto Veneto Anziani (Pro.V.A.) study. The baseline serum 25OHD levels were categorized as <24, 25-49, 50-74, >75 nmol/L, and incident PAD was defined as an ankle-brachial index below 0.9.

Results: At the baseline, there were no differences in known risk factors for PAD (BMI, waist circumference, diabetes, cardiovascular diseases, smoking habits, total cholesterol) or in the ankle-brachial index (ABI) between the groups with different serum 25OHD levels (<24, 25-49, 50-74, >75 nmol/L). During a 4.4-year follow-up, 371 subjects developed PAD. The group with serum 25OHD levels >75 nmol/L was set as the reference group, and an adjusted Cox's regression analysis showed no association between low vitamin D levels and incident PAD during the follow-up: the hazard ratio ranged from 0.76 (95%CI: 0.41-1.42) for participants with serum 25OHD levels below 25 nmol/L to 1.32 (95%CI: 0.72-2.39) for those with serum 25OHD levels between 50-74 nmol/L (*p* for trend=0.08). These results did not change when participants were stratified by several risk factors for PAD.

Conclusions: Baseline hypovitaminosis D did not predict the onset of PAD over a 4.4-year follow-up in elderly people.

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Key words: Peripheral artery disease, Vitamin D, Elderly, Cardiovascular disease

Introduction

Peripheral artery disease (PAD) is a common

condition in the elderly and associated with a high risk of disability, further morbidities, and mortality¹. Besides the established risk factors for PAD (e.g., dyslipidemia, diabetes mellitus, hypertension, smoking, decline in renal function, and inflammatory conditions), a poor vitamin D status has been gaining increasing interest.

Animal and *in vitro* models have suggested that vitamin D has anticoagulant properties, suppresses the

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proliferation of vascular smooth muscle cells, and improves endothelial vasodilation - hence the hypothesis of a pathophysiological role of vitamin D deficiency in promoting atherosclerotic processes²⁻⁷).

Cross-sectional studies have shown a strong association between low serum 25-hydroxyvitamin D (25OHD) levels and PAD in middle-aged and older people⁷⁻¹². The nature of these studies makes it impossible to say, however, whether low vitamin D status precedes or follows the onset of PAD. It is important to confirm or reject any causal role of vitamin D status in PAD because low serum 25OHD levels are readily reversible.

Meanwhile, recent literature has indicated that the association between hypovitaminosis D and other metabolic and cardiovascular diseases (CVD) appears to be weaker in the elderly than in the middle-aged¹³⁻¹⁵. This may be for several reasons, including a physiological decline in vitamin D receptor expression with aging¹⁶ and a different role for low vitamin D levels in the elderly vis-à-vis younger adults. Given these premises, we hypothesized that no direct relationship exists between low serum 25OHD levels and incident PAD in elderly people.

Aim

The aim of the present study was thus to examine whether low serum 25OHD levels were associated with a higher risk of incident PAD over a lengthy follow-up (4.4 years) in a representative group of elderly men and women.

Materials and Methods

Data Source and Subjects

Data for this study came from the *Progetto Veneto Anziani* (Pro.V.A.), an observational cohort study on an Italian population comprised over 65 years of age. The study population included 3,099 age- and sex-stratified Caucasian participants (1,854 women and 1,245 men) who were randomly selected between 1995 and 1997 using a multistage stratified method. The sampling procedures and data collection methods have been extensively described elsewhere¹⁷. Trained physicians and nurses examined the patients at outpatient clinics. This study concerns the information obtained on the incidence of PAD, as assessed over a mean ($\pm$ SD) 4.4 ± 1.2 years of follow-up.

204 of the 3,099 subjects initially enrolled in the study were excluded because no data were available on their serum 25OHD levels (the study inclusion criteria are summarized in **Fig. 1**). We additionally

Fig. 1. Diagram of the study population selection

excluded 798 participants because they already had PAD at the baseline (38 of them had an ankle-brachial index [ABI] ≥ 1.5 reflecting a severe arterial rigidity). Among the remaining 2,097 participants, there were 1,568 patients who had data available on any PAD diagnosed at the follow-up visit (while 380 had died, and data were missing for 149).

The local ethical committees of Padua University and the Veneto Region's Local Health Units (USSL) n. 15 and n. 18 approved the study protocol, and participants gave their written informed consent.

Clinical Data

The participants were examined at city hospitals by trained physicians and nurses. During a face-to-face interview, information was collected on their formal education, monthly income, physical activity, alcohol consumption, smoking history, and drug history. Education was categorized as five or less years vs. more than five years of schooling because 5 years of school attendance was the compulsory minimum when our sample population was of primary school age. Socio-economic condition was categorized as a monthly income below or above 500 €. Smoking

habits were categorized as “never” vs. “former” (having stopped smoking at least a year previously) or “current” smoking. Regular physical activity was defined as ≥ 4 hr/week during the previous month of at least moderate physical activity (e.g., brisk walking, cycling, gardening, dancing, or physical exercising). The body weight and height were measured by trained physicians, the body mass index (kg/m^2) was calculated, and the waist circumference was recorded. Clinostatic systolic and diastolic blood pressures were recorded as the mean of three readings obtained while the subject remained supine.

Any diseases were ascertained by board-certified physicians involved in the study who examined all of the clinical information collected for each participant, including their disease history, self-reported symptoms (using standardized questionnaires), medical and hospital records, blood tests, and physical examinations¹⁷.

Definition of Incident PAD

The primary outcome for the purposes of the present study was PAD as defined by the means of the ABI measured at the participants' baseline and follow-up visits. To calculate the ABI, systolic blood pressure was measured with blood pressure cuffs on the right brachial artery and both posterior tibial arteries using a method similar to the one applied in the NHANES study¹⁰. Two measurements were taken and averaged at each site. For individuals with conditions precluding measurements of the right arm, the systolic blood pressure was measured on the left brachial artery. The ABI was calculated as the ratio between the average ankle and arm systolic blood pressures. The smaller of the 2 ABI was considered as the value for this study and the presence of PAD was identified as an ABI lower than 0.9. Any presence of claudication was assessed on the grounds of inducing pain which kept participants from covering at least 200 m during the 6-minute walk test¹⁸.

Laboratory Data

A venous blood sample was obtained after an overnight fast for the biochemical tests, which were performed at the central laboratory of Padova Hospital (using standard and quality-controlled procedures).

Glycosylated hemoglobin (HbA1c) was measured using high-performance liquid chromatography (HPLC). Serum 25OHD levels were measured by radioimmunoassay (RIA kit; DiaSorin). The intra-assay and inter-assay coefficients of variation (CVs) for serum 25OHD levels were 8.1% and 10.2%, respectively. Serum intact PTH levels were measured using a two-site immunoradiometric assay kit (N-tact

PTHSP; DiaSorin): the intra-assay and inter-assay CV for PTH were 3.0% and 5.5%, respectively. The serum calcium level was measured with an anion-specific electrode obtaining an intra-assay and inter-assay CV of 1.0% and 2.2%, respectively. The blood collection season was defined as winter, spring, summer, or autumn. Serum creatinine levels were measured with the Jaffe reaction via the Roche Hitachi autoanalyzer (Roche Diagnostic GmbH, Mannheim, Germany) calibrated using the uncompensated method. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. The total cholesterol, triglycerides, and high-density lipoproteins (HDL) were calculated using an enzymatic method and serum low-density lipoproteins (LDL) were calculated using Friedwald's formula unless the serum triglycerides were over 400 mg/dl (as was the case in 16 participants). Dyslipidemia was diagnosed using the following cut-offs: serum HDL levels <40 in women and 50 mg/dl in men; triglycerides >150 mg/dl; LDL >160 mg/dl; or total cholesterol >200 mg/dl¹⁹. The erythrocyte sedimentation rate (ESR) was measured by the Westergren method using sodium citrate anticoagulant. An inflammatory status was defined as an ESR over 40 mm/h based on the upper limit available at our laboratory.

Statistical Analyses

The participants' characteristics were summarized using means ($\pm$ standard deviations) for continuous variables and counts and percentages for categorical variables. For the continuous variables, normal distributions were tested using the Shapiro-Wilk test. Age- and gender-adjusted *p* values for trends were calculated using a general linear model for the continuous variables and logistic regression analysis for the categorical variables. The means and proportions were compared between study participants according to their baseline serum 25OHD values (grouped as <24 , 25 - 49 , 50 - 74 , >75)²⁰ using the Bonferroni correction where necessary.

The age-standardized incidence of PAD was calculated as the number of new cases per 1000 person-years during the follow-up, standardized according to the age structure of the Italian population in 1991, and compared using a logistic binary regression analysis.

Cox's proportional hazards models were used to assess associations between the 25OHD groups and incident PAD. Factors known to be associated with the serum 25OHD levels and/or PAD were examined for inclusion in the analysis. To explore whether vari-

ables should be included as predictors in the final survival model, we performed the log-rank test of equality across strata for all the categorical variables and Cox's univariate proportional hazards regression for all the continuous variables. The predictors included in the final model were all the variables with a $p < 0.20$ in the univariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to compare the rates of PAD across different 25OHD groups; serum 25OHD levels above 75 nmol/L was set as the reference group. The Wald test was used to calculate p values for trend based on a score with the median value of each serum 25OHD group. Although serum PTH showed a high collinearity with the serum 25OHD levels (as quantified by the variance inflation factor=4.25), this variable was included in the final model because previous research had identified an independent effect of serum 25OHD levels on the onset of cardiovascular disease¹².

We conducted several sensitivity analyses, stratifying for known clinical factors independently associated with PAD¹⁸, to check whether the association between serum 25OHD and PAD depends on any medical or other conditions.

All analyses were performed using the SPSS statistical software package (version 21.0 for Windows; SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and a p value < 0.05 was considered to be statistically significant.

Results

Baseline Characteristics

Compared with the sample population included in this analysis, the participants who dropped out or died were more likely to be men (50.9% vs. 34.1%; $p < 0.0001$) and older (81.67 ± 7.70 vs. 74.16 ± 6.92 ; $p < 0.0001$). After adjusting for age and sex, those without follow-up data were more likely to have a diagnosis of cardiovascular disease (9.1% vs. 2.8%) and/or diabetes (20.4% vs. 13.5%) at the baseline, as well as significantly lower serum 25OHD levels (68.23 ± 54.73 vs. 80.80 ± 45.56 nmol/L) and ABI (1.00 ± 0.09 vs. 1.12 ± 0.10) ($p < 0.0001$ for all comparisons).

The sample population analyzed here consisted of 1,568 community-dwelling elderly subjects with no PAD at the baseline. They had a mean age of 74.0 ± 6.6 years (range: 65-94 years), a mean BMI of 27.91 ± 4.61 kg/m², and the majority were women (66%). Their mean serum 25OHD level was 80.80 ± 45.56 nmol/L and their mean ABI 1.12 ± 0.10 . Both parameters were significantly higher in men than in women (103.48 ± 50.13 vs. 69.58 ± 38.49 nmol/L, $p < 0.0001$

for serum 25OHD and 1.14 ± 0.10 vs. 1.12 ± 0.10 , $p < 0.0001$ for ABI).

Participants in the lowest 25OHD group were significantly older and more likely to be women than those in the highest serum 25OHD group (p for trend < 0.0001 for both variables). After adjusting for age and gender, participants in the lowest serum 25OHD group were found to be better educated (p for trend = 0.002), less active (p for trend = 0.003), and consumed more alcohol (p for trend = 0.04). Additionally, more blood collections had been obtained from these participants during the winter season than from the groups with higher serum 25OHD levels (p for trend = 0.002) (Table 1).

As for possible risk factors for PAD at the baseline, there were no differences in the prevalence of diabetes (p for trend = 0.34), CVD (p for trend = 0.06), hypertension (p for trend = 0.69), or "current" smoking (p for trend = 0.14) across the serum 25OHD groups. Among the biohumoral tests related to PAD, only the ESR was found to be significantly higher among participants with serum 25OHD levels < 24 nmol/L (p for trend = 0.001). The baseline ABI was also similar across the serum 25OHD groups (p for trend = 0.54).

Follow-Up Data

During a follow-up of 4.4 years, 371 (121 men and 250 women) new cases of PAD were recorded, and 134 of those cases had claudication. The incidence rate in the sample population overall was 54 new cases per 1000 person-years and was highest in the group with serum 25OHD levels < 24 nmol/L (72; 95%CI: 25-119), although the incidence rate did not differ significantly between the serum 25OHD groups (p for trend = 0.86) (Table 2). Moreover, the baseline serum 25OHD levels were similar in participants who were diagnosed with PAD at the follow-up visit and those who were not (81.85 ± 45.12 vs. 77.42 ± 46.85 nmol/L, $p = 0.48$, after adjusting for age and sex).

Using Cox's regression analysis, and adjusting for potential confounders, serum 25OHD levels < 24 , 25-49, or 50-74 nmol/L did not indicate a higher probability of having PAD. The HRs ranged from 0.76 (95%CI: 0.41-1.42) for the group with serum 25OHD levels < 24 nmol/L to 1.32 (95%CI: 0.72-2.39) in the group with serum 25OHD levels between 50 and 74 nmol/L (p for trend = 0.08) (Table 2).

As shown in Fig. 2, the results of all our statistical analyses remained differ significantly after stratifying participants by age, gender, smoking habits, presence or absence of hypertension, dyslipidemia, inflam-

Table 1. Participants' characteristics by serum 25-hydroxyvitamin D (25OHD) cut-offs of 25, 50 and 75 nmol/L

Variable	< 24 nmol/L (n = 115)	25-49 nmol/L (n = 322)	50-74 nmol/L (n = 380)	> 75 nmol/L (n = 751)	p value*
Age (years)	77.30 ± 6.90	75.18 ± 7.22	74.11 ± 6.55	72.17 ± 5.93	< 0.0001 [†]
Female sex (%)	86.1	82.3	77.1	52.5	< 0.0001 [†]
Anthropometric and demographic data					
BMI (kg/m ²)	28.40 ± 5.69	28.05 ± 4.98	28.41 ± 4.40	27.53 ± 4.34	0.13
Waist circumference (cm)	96.23 ± 13.59	95.99 ± 12.03	97.29 ± 11.46	95.88 ± 10.77	0.07
Education ≥ 5 yrs (%)	15.8	15.8	13.2	14.9	0.002
Monthly income ≤ 500 € (%)	32.1	32.5	36.7	39.2	0.26
Current smokers (%)	7.8	6.8	8.4	9.5	0.14
Previous/non-smokers (%)	12.2	16.5	20.5	33.7	0.24
Physical activity ≥ 4 hr/week (%)	12.2	19.3	23.4	31.3	0.003
Alcohol drinkers (%)	60.0	60.6	68.4	76.0	0.04
Blood pressure characteristics					
Hypertension (%)	67.0	73.9	69.7	69.2	0.69
Anti-hypertensive drugs (%)	60.4	60.1	59.5	57.5	0.33
Systolic BP (mmHg)	152.74 ± 22.51	152.97 ± 21.13	151.40 ± 19.79	151.72 ± 20.40	0.81
Diastolic BP (mmHg)	81.73 ± 10.91	83.58 ± 10.80	82.76 ± 10.19	83.88 ± 10.37	0.47
ABI	1.11 ± 0.09	1.11 ± 0.09	1.13 ± 0.10	1.12 ± 0.10	0.54
Medical conditions and drugs					
Diabetes (%)	11.3	13.4	12.9	13.2	0.34
CVD (%)	6.1	3.4	2.6	1.7	0.06
Vitamin D supplementation (%)	3.5	1.9	1.6	0.9	0.29
Anti-diabetic drugs (%)	7.9	8.3	7.5	6.6	0.80
Low-dose aspirin (%)	8.9	11.5	7.2	9.3	0.68
Statin use (%)	2.0	3.6	4.9	1.6	0.20
Biohumoral tests					
HbA1c (%)	5.29 ± 1.07	5.35 ± 1.00	5.43 ± 1.22	5.13 ± 0.84	0.03
25OHD (nmol/L)	17.60 ± 5.27	39.12 ± 6.99	62.57 ± 7.32	106.00 ± 37.47	< 0.0001
PTH (ng/l)	56.29 ± 46.10	43.81 ± 22.02	41.52 ± 18.84	35.79 ± 24.11	< 0.0001
Calcium (mg/dl)	9.35 ± 0.47	9.48 ± 0.47	9.48 ± 0.47	9.46 ± 0.55	0.07
eGFR (ml/min)	69.51 ± 18.06	67.65 ± 18.80	68.47 ± 17.02	72.99 ± 16.95	0.14
ESR (mm/h)	26.70 ± 20.25	20.69 ± 15.65	21.01 ± 15.87	15.97 ± 16.24	0.001
Total cholesterol (mg/dl)	236.87 ± 45.73	238.75 ± 44.58	240.84 ± 42.85	232.21 ± 41.22	0.33
HDL (mg/dl)	59.25 ± 14.62	59.97 ± 15.61	57.01 ± 14.72	59.26 ± 17.84	0.12
LDL (mg/dl)	152.00 ± 37.89	152.02 ± 37.13	155.97 ± 36.95	148.02 ± 35.45	0.12
Triglycerides (mg/dl)	138.85 ± 72.02	140.96 ± 74.85	140.83 ± 69.77	129.52 ± 73.74	0.10
Blood collection in the winter	36.5	28.9	20.3	20.0	0.002
Blood collection in the spring	20.9	28.9	24.7	30.9	
Blood collection in the summer	18.3	19.3	21.8	18.2	
Blood collection in the autumn	24.3	23.0	33.2	30.9	

Notes:

The numbers are listed as the mean values (standard deviations) or percentages (%) as appropriate.

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

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

Abbreviations: BMI: body mass index; BP: blood pressure; ABI: ankle-brachial index; CVD: cardiovascular diseases; HbA1c: glycosylated hemoglobin; 25OHD: serum 25-hydroxyvitamin D; PTH: parathormone; eGFR: estimated glomerular filtration rate; HDL: high-density lipoproteins; LDL: low-density lipoproteins.

Table 2. Associations between serum 25-hydroxyvitamin D concentrations and incident peripheral artery disease

Incidence parameters	>75 nmol/L	50-74 nmol/L	25-49 nmol/L	< 24 nmol/L	P for trend
Number of cases	165	90	75	41	-
Total number	751	380	322	115	-
Age-adjusted incidence*	49 (33-65)	53 (31-75)	42 (21-63)	72 (25-119)	0.86
Hazard ratio	>75 nmol/L	50-74 nmol/L	25-49 nmol/L	< 24 nmol/L	P for trend
Unadjusted	1	1.03 (0.69-1.53)	0.83 (0.53-1.28)	1.18 (0.70-1.98)	0.92
Age- and sex-adjusted model	1	1.15 (0.67-1.96)	0.97 (0.56-1.70)	0.71 (0.40-1.27)	0.06
Fully-adjusted model [†]	1	1.32 (0.72-2.39)	1.00 (0.54-1.87)	0.76 (0.41-1.42)	0.08

Unless otherwise specified, the data are presented as relative risks and 95% confidence intervals.

Notes:

*Incidence rates are per 1000 person-years. The data are expressed as means with 95% confidence intervals and compared with a logistic regression analysis using age and sex as covariates.

[†]Fully-adjusted model: age, sex, waist circumference, education and physical activity, smoking habits, alcohol drinking; baseline ABI, systolic and diastolic blood pressure; diabetes, hypertension, CVD; use of statins, low-dose aspirin, vitamin D supplementation; serum levels of total cholesterol, HDL cholesterol, HbA1c, eGFR, ESR; season of blood collection.

mation, impaired renal function, or diabetes. Finally, using sex-specific serum 25OHD quartiles or sex-specific serum PTH quartiles instead of serum 25OHD did not modify our results (data not shown).

Discussion

Our large population-based prospective study found no evidence of any significant association between serum 25OHD levels and incident PAD over a follow-up of 4.4 years. These findings were non influenced by the presence or absence of known risk factors for PAD.

About half of the participants in our study had serum 25OHD levels higher than 75 nmol/L, while one in three had levels below 50 nmol/L. These relatively high vitamin D concentrations in our population are probably due to the inclusion of both sexes in our groups and to their provenance from a geographical area where outdoor activities are widespread²¹. Our sample population's serum 25OHD levels were comparable with those seen in another large study²² conducted during the same period. Conversely, we found an incidence rate of 54 new cases of PAD per 1000 person-years, which is five times higher than the figure previously reported by Hooi *et al.* in a study investigating the incidence of PAD in a cohort that was a mean 10 years younger than our population²³. This very large difference is probably due to the difference in age between the two studies: our sample population had a mean age of 74 years, and the incidence of PAD is known to rise exponentially with aging, especially beyond 75 years of age^{24, 25}.

Several cross-sectional studies have found a low

vitamin D status associated with a higher prevalence of PAD which would support a pathophysiological role for vitamin D status in this disease⁷⁻¹². We, however, found no such significant prospective association between low serum 25OHD levels and incident PAD. There may be several reasons for this discrepancy. First, the vitamin D receptor expression declines linearly with age²⁶, indicating that extremely high levels of serum 25OHD would probably be necessary in the elderly to have any substantial effect in preventing atherosclerotic processes. Second, low serum 25OHD levels are indicative of a high risk of death among the elderly²⁷. In fact, the patients in our study who died during the study period not only had significantly lower serum 25OHD levels than the other participants but also had a significantly lower baseline ABI. Thus, many participants with low serum 25OHD levels may have died before developing PAD. Finally, in the cross-sectional studies, it may be that participants with PAD were less mobile and had comorbidities that led to being less exposed to sunlight and consequently having lower serum 25OHD levels than participants without PAD.

Our study also failed to find an association between the baseline serum PTH levels and incident PAD. Several observational studies have suggested that high serum PTH levels are associated with hypertension and myocardial dysfunction and may promote the onset of fatal and non-fatal CVD events²⁸. A pathophysiological role of PTH in PAD is sustained by the evidence that high PTH levels are associated with vascular calcifications, especially in patients with an impaired renal function²⁸. Nonetheless, we failed to find any significant association between PTH and

Fig. 2. Adjusted hazard ratios (for the same covariates as in Table 2) by the presence/absence of known risk factors for the onset of PAD by serum 25-hydroxyvitamin D levels

the onset of PAD in our cohort, which is supported by a recent study on the possible association between PTH and incident CVD events²⁹.

There are both strengths and limitations associated with this study. The main limitation is that the serum 25OHD concentration was only measured at the baseline, and this may not reflect our participants' follow-up vitamin D status, although serum 25OHD levels drop extremely slowly even in the elderly^{30, 31}. Because the use of vitamin supplementation was reportedly extremely limited in our sample popula-

tion, at both the baseline and the follow-up visits (1.5% and 3.1%, respectively), we are confident that our results were negligibly influenced by our failure to measure the serum 25OHD levels at the follow-up visit. Moreover, serum phosphorus levels were not measured, although hyperphosphoremia appears to be an independent risk factor for CVD³². We also did not assess ABI in other ways (e.g., toe pressure versus ankle pressure) in diabetic participants or patients with diseases at high risk of vascular calcifications¹⁸. Another important limitation is that we only consid-

ered Caucasian people, although it is well known that racial differences exist in both serum 25OHD levels and ABI¹¹⁾. This means that studies conducted on different ethnic groups may generate very different findings. Finally, we did not consider C-reactive protein (CRP) levels among the covariates strongly associated with PAD³³⁾, though we did measure ESR, which is a good proxy of CRP for inflammation. The main strengths of our work are that we considered the ABI (which is the most precise method for identifying PAD), used a longitudinal design, and followed our patients over a long period of time which enabled us to identify 371 new cases of incident PAD (which was approximately a quarter of the population considered at the baseline). Another strength is the use of serum 25OHD, which is the best indicator of the total body stores of vitamin D, and the large number of potential confounders analyzed.

Conclusion

The baseline serum concentrations of 25OHD were not associated with the incidence of PAD over a 4.4-year follow-up in our sample population of elderly people. Because PAD is an increasingly common disease in the elderly, and associated with several important complications (e.g., amputation, disability and mortality), the exact role of vitamin D in this disease should be further clarified in randomized clinical trials.

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Conflicts of Interest

The authors declare no conflicts of interest (COI).

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