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Vitamin D deficiency and cardiovascular diseases: results from the Neyshabur Longitudinal Study on Ageing

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Abstract

Objectives: This study aimed to investigate the relationship between Vitamin D levels and Cardiovascular Diseases (CVDs) such as myocardial infarction (MI), stroke, and angina.

Methods: Data for this cross-sectional study were collected as part of the Neyshabur Longitudinal Study on Ageing (NeLSA) between 2016 and 2018. The effect of Vitamin D on CVDs was analyzed in conjunction with socioeconomic and medical history variables. Statistical analysis was conducted using the Chi-square test and logistic regression in the R.

Results: Vitamin D levels were evaluated in 3414 participants (1527 men and 1889 women), with over two-thirds of participants showing insufficiency or deficiency of Vitamin D. Among them, 362 participants had self-reported diagnosed CADs. The study did not find a significant association between serum 25OH Vitamin D levels and the risk of CADs. Adjusted logistic regression revealed that male gender was a risk factor for MI (OR=4.7; 95% CI: 3.125-6), stroke (OR=1.75; 95% CI: 1.08-2.85), and angina (OR=1.6; 95% CI: 1.03-2.7). Additionally, having one or more medical conditions other than hypertension and diabetes was associated with angina (OR=7.14; 95% CI: 3.7-14.7), MI (OR=5; 95% CI: 2.97-8.3), and stroke (OR=2.7; 95% CI: 1.2-4.7). Participants aged over 70 years were more likely to experience angina (OR=2.43; 95% CI: 1.36-4.5) and stroke (OR=2.5; 95% CI: 1.35-4.5).

Conclusions: The study revealed a high prevalence of Vitamin D deficiency and insufficiency. While the protective role of Vitamin D against CADs was not supported in this study, it does not discount the potential benefits of Vitamin D supplementation for overall health in older individuals.

Keywords: Ageing, Vitamin D, Cardiovascular diseases.

Introduction

Vitamin D is a fat-soluble pro-hormone that plays a pivotal role in bone homeostasis, calcium metabolism, modulation of cell growth, neuromuscular and immune function, and reduction of inflammation.[1] The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D), acts as a steroid hormone by binding to the vitamin D receptor (VDR), which is present in many body cells including cardiomyocytes, vascular smooth muscle, and endothelium.[2] The American guidelines for the evaluation, prevention, and treatment of vitamin D deficiency establish that the body pool of the vitamin should be determined by measuring serum 25-hydroxyvitamin D with the following cut-off points: 1) Deficiency when below or equal to 20 ng/mL, 2) Insufficiency when between 20 and 30 ng/mL, and 3) Sufficiency when greater than 30 ng/mL.[3]

Vitamin D deficiency (VDD) is widespread, especially among older women living in higher latitudes with less sunlight exposure. It has been estimated that the prevalence of VDD is approximately 30–50% in the general population. VDD has been linked to

cardiovascular diseases (CVDs).[4] Previous studies have not provided a clear understanding of the relationship between VDD and CVDs. For example, a study by Thompson et al., a large sample size clinical trial, showed a reduced risk of CVDs among elderly participants with vitamin D supplementation compared to the control (placebo) group.[5] However, a comprehensive meta-analysis collecting data from 21 clinical trials indicated that vitamin D may not function as a protective factor against CVDs.[6]

Meanwhile, CVDs are the prevalent cause of morbidity and mortality worldwide, affecting millions of individuals every year, particularly the elderly.[7] The World Health Organization estimates that 31 percent of all global deaths are due to CVDs.[8] The mechanism by which vitamin D may protect individuals from CVDs has not been fully elucidated. Several mechanisms have been proposed, including negatively regulating renin to lower blood pressure,[9] improving vascular compliance,[10] decreasing parathyroid hormone levels,[11] and improving glycemic control.

Objectives

Therefore, this study aims to investigate the association between vitamin D and CVDs in older individuals based on data gathered in the registration phase of the Neyshabur Longitudinal Study on Ageing.

Methods

The Neyshabur Longitudinal Study on Ageing (NeLSA) is an elderly component of the Prospective Epidemiological Research Studies in Iran (PERSIAN) that was initiated in 2014. NeLSA was the first comprehensive longitudinal study on ageing among individuals aged 50-94 years in Iran. Its primary objective was to assess various aspects of ageing, monitor changes in the health and wellbeing of older adults, and gather a wide range of data through comprehensive questionnaires covering demographic, socioeconomic, lifestyle, physical, and psychological aspects. Additionally, clinical examinations were conducted on biological samples (blood, urine, nail, and hair), mobility assessments, and anthropometric measures. The details of the cohort study were recently published by Aminisani et al. (2022).[12]

For this study, data from the registration phase of the NeLSA study conducted between 2016-2018 were utilized in a cross-sectional design. In summary, participants of NeLSA were residents of Neyshabur aged 50–95 years who had been living in Neyshabur for a minimum of three years, were Iranian citizens (verified by national ID card and birth certificate), and did not have dementia, major depression, or disabilities that could limit their participation in the study. Individuals with conditions such as diabetes mellitus, liver or renal disease, malignancy, hyper- or hypoparathyroidism, vitamin D supplements, or medications that affect vitamin D metabolism (e.g., lipid-lowering drugs) were excluded from the study.

The serum level of vitamin D was measured in individuals who participated in the comprehensive phase of the study. Vitamin D deficiency was defined according to the Clinical Practice Guidelines from the US Endocrine Society as serum 25-OH D <50 nmol/l (below 20 ng/ml). Vitamin D insufficiency was considered for serum levels of 25-OH D ranging between 50 and 75 nmol/l (21–29 ng/ml), while normal range was defined as >30 ng/ml.

Myocardial Infarction (MI), Stroke

Participants self-reported doctor-diagnosed MI or stroke through a question asking if they had ever been told by a doctor that they had experienced a MI/Stroke. Positive responses were verified with medical records and medications. Angina pectoris was operationalized using the WHO Rose questionnaire criteria, which includes symptoms worsened by exertion, relieved by rest or nitrates, and located on the sternum, left side of the chest, or left arm during the last 12 months. Participants who answered affirmatively to any of these questions were coded as having angina pectoris. Data on predictors of CVDs such as physical activity, smoking status, cholesterol levels, BMI, hypertension, diabetes, and other medical conditions were also collected.

Statistical analysis

Chi-square tests were used to compare sociodemographic characteristics and serum vitamin D levels. The relationship between individual factors and outcome measures (MI, Angina, stroke) was assessed using crude logistic regression. Independent associations of risk factors were examined through adjusted logistic regression. Statistical significance was set at p value<0.05. Data analysis was performed using R version 3.6.1.

Ethical consideration

This study received ethical approval from the Ethics Committee of Neyshabur University of Medical Sciences (reference number: IR.NUMS.REC.1400.010). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects and/or their legal guardians.

Results

Out of the 4,104 participants invited to take part in the NeLSA cohort study at baseline, 3,416 were deemed eligible, with 1,527 (44.7%) being men and 1,889 (55.3%) women, most of whom were in the 50-59 age group. Table 1 presents the descriptive characteristics of the participants. Only 31.7% of the total participants had sufficient plasma 25(OH) vitamin D, while 26% and 42.3% were found to have insufficiency and deficiency of vitamin D, respectively. Age, gender, smoking, cholesterol level, medical conditions, and physical activity were observed to influence serum vitamin D levels significantly (p-value<0.05). Conversely, no differences in vitamin D deficiency were noted concerning BMI, hypertension, and diabetes [Table 1].

The frequency distribution of vitamin D deficiency in relation to stroke, MI, and angina is depicted in Figure 1. Among all participants included, 103 were diagnosed with stroke, 152 with MI, and 107 with angina. Notably, there was no significant difference in the number of cardiovascular patients based on vitamin D levels (sufficient, insufficient, and deficient).

Logistic regression analysis was conducted to explore the crude and adjusted associations between vitamin D levels and cardiovascular diseases while considering other health predictors [Table 2]. In both crude and adjusted models, no significant association was found between vitamin D levels and the risk of cardiovascular disorders, including angina, Myocardial Infarction (MI), and stroke.

In univariate analysis, factors such as male gender (OR=1.12; 95% CI: 0.78-1.69), age over 70 (OR=2.7; 95% CI: 1.63-3.7), high cholesterol (OR=1.44; 95% CI: 1.08-1.96), and having other medical conditions (OR=6.6; 95% CI: 3.7-12.5) were associated with an increased risk of angina. Additionally, having more than one medical condition served as a strong predictor of angina. Conversely, diabetes (Odds ratio [OR]=0.56; confidence interval [95% CI]= 0.3-0.84) was negatively associated with angina. Compared to those without MI, individuals aged over 70 years (OR=2.56; 95% CI: 1.63-4.1), males (OR=2.89; 95% CI: 2.04-4.1), participants with high cholesterol (OR=1.56; 95% CI: 1.23-2), and those with one (OR=4; 95% CI: 3.1-6.25) or more medical conditions (OR=4; 95% CI=3.1-6.25) were more likely to have MI. Similarly, factors increasing the risk of stroke included age over 70 years (OR=3.14; 95% CI: 1.85-5.54), male gender (OR=1.5; 95% CI: 1.02-2.27), high blood cholesterol levels (OR=1.44; 95% CI: 1.09-1.92), having one (OR=2.94; 95% CI: 1-1.81) or more medical conditions (OR=2.94; 95% CI: 1.1-3.81), and low physical activity (OR=1.94; 95% CI:

1.19-3.18). However, cardiovascular disorders were not associated with variables such as obesity, hypertension, and smoking.

In the adjusted model, male gender emerged as a strong predictor for an increased risk of cardiovascular disorders among the elderly population. Specifically, the risk of angina, MI, and stroke in males was respectively 1.6, 4.7, and 1.75 times higher than in females. Additionally, having medical conditions other than hypertension and diabetes showed a notable positive association with angina (OR=7.14; 95% CI: 3.7-14.7), MI (OR=5; 95% CI: 2.97-8.3), and stroke (OR=2.7; 95% CI: 1.2-4.7). Furthermore, age over 70 years was identified as a risk factor for angina (OR=2.43; 95% CI: 1.36-4.5) and stroke (OR=2.5; 95% CI: 1.35-4.5).
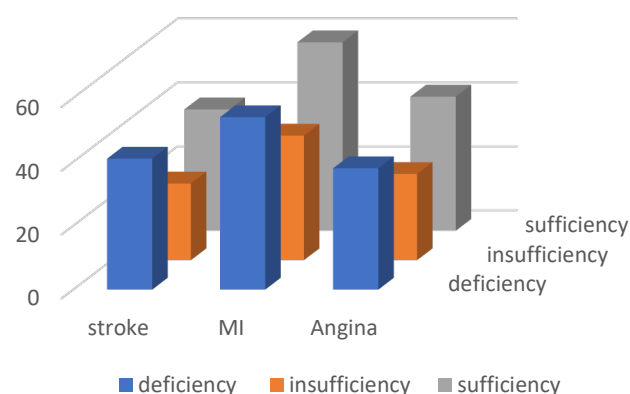

Figure 1. The frequency distribution of vitamin D deficiency under cardiovascular disease

Discussion

Vitamin D deficiency is a prevalent health issue associated with numerous serious skeletal and non-skeletal consequences. Low plasma 25(OH) vitamin D levels have been linked to various chronic conditions, including genetic, metabolic, cognitive, and skeletal disorders, particularly affecting the elderly population.[13-15] Our study revealed that a significant proportion of participants (over 68%) experienced vitamin D deficiency or insufficiency. Consistent with our findings, Iranian adults have also been reported to have high rates of Vitamin D deficiency,[13,16] with similar trends observed in other Middle Eastern countries.[17] Interestingly, we observed a lower prevalence of Vitamin D deficiency among individuals aged over 70 years, potentially attributed to vitamin D supplementation practices in this age group. The implementation of vitamin D supplementation programs has been recognized as a crucial strategy to mitigate Vitamin D deficiency and its

associated health risks.[13]

Key factors associated with Vitamin D deficiency in the elderly population identified in our study included age, gender, smoking, cholesterol levels, existing medical conditions, and physical activity. Previous research has highlighted a wide range of determinants for Vitamin D deficiency, with primary factors encompassing low sun exposure,[17] lack of vitamin D supplementation, non-white ethnicity, specific genetic variations,[18] environmental exposures,[19] smoking, poor health status, and obesity.[20]

Table1. Baseline characteristics of study participants.

Parameters	Total	Vitamin D deficiency (N=1446)	Vitamin D insufficiency (N=888)	Vitamin D sufficiency (N=1082)	P value
Age					<0.001*
50-59	1621(51%)	754(56%)	432(52.2%)	435(43.2%)	
60-69	1006(31.6%)	410(30.4%)	264(31.9%)	332(33%)	
>=70	553(17.4%)	183(13.6%)	131(15.8%)	239(23.8%)	
Gender					0.001*
Male	1552(45.4%)	647(44.7%)	450(50.7%)	445(42.1%)	
Female	1864(54.6%)	799(55.3%)	438(49.3%)	627(57.9%)	
Smoking					<0.001*
Yes	372(11%)	178(12.4%)	111(12.7%)	83(8.7%)	
No	3004(89%)	1253(87.6%)	765(87.3%)	986(92.2%)	
BMI					0.943
Normal (BMI<25)	921(27.4%)	380(26.6%)	241(27.3%)	300(28.4%)	
Overweight(25<=BMI<30)	1414(42%)	595(41.7%)	374(42.3%)	445(42.1%)	
Obese (BMI>=30)	1032(30.7%)	451(31.6%)	269(30.4%)	312(29.5%)	
Hypertension					0.086
yes	447(13.1%)	206(14.2%)	119(13.4%)	960(87.7%)	
No	2969(86.9%)	1240(85.5%)	769(86.6%)	122(11.3%)	
High Cholesterol					<0.001*
Yes (>140)	639(18.8%)	311(21.6%)	164(18.5%)	164(15.2%)	
No	2768(81.2%)	1130(78.4%)	722(81.5%)	916(84.8%)	
Diabetes					0.805
Yes	901(26.4%)	378(26.2%)	230(25.9%)	293(27.1%)	
No	2513(73.6%)	1067(73.8%)	657(74.1%)	788(72.9%)	
Stroke					0.504
Yes	103(3%)	41(2.8%)	24(2.7%)	38(3.5%)	
No	3313(97%)	1405(97.2%)	864(97.3%)	1044(96.5%)	
MI					0.116
Yes	152(4.4%)	54(3.7%)	39(4.4%)	59(5.5%)	
No	3264(95.6%)	1392(96.3%)	849(95.6%)	1023(94.5%)	
Angina pectoris					0.198
Yes	107(3.1%)	38(2.6%)	27(3%)	42(3.9%)	
No	3309(96.9%)	1408(97.4%)	861(97%)	1040(96.1%)	
Other medical conditions					<0.001*
None	1101(32.2%)	454(37.7%)	293(33%)	263(24.3%)	
One	2315(67.8%)	856(62.3%)	595(67%)	819(75.7%)	
PASE					<0.001*
Low tertile (<=35.82)	1287(37.8%)	507(35.2%)	350(39.5%)	430(39.9%)	
Middle tertile (35.82-71.98)	959(28.2%)	408(28.3%)	215(24.3%)	336(31.2%)	
High tertile (>=71.98)	1157(34%)	526(36.5%)	320(36.2%)	311(28.9%)	

*Statistically significant

Table 2. Logistic regression for associations between cardiovascular disease and risk factors

Parameters	Angina		Myocardial infarction		Stroke	
Vit D	OR**(95%CI)	OR*** (95%CI)	OR**(95%CI)	OR***(95%CI)	OR**(95%CI)	OR***(95%CI)
Sufficiency						
Deficiency	0.66(0.42-1.04)	0.95(0.58-1.57)	0.67(0.46-0.97)	1.004(0.64-1.57)	0.8(0.5-1.25)	1.26(0.76-2.07)
Insufficiency	0.77(0.47-1.27)	0.96(0.56-1.24)	0.79(0.52-1.2)	1.18(0.74-1.9)	0.76(0.45-1.28)	0.98(0.56-1.07)
Age						
50-59(ref)						
60-69	1.29(0.78-2.12)	1.36(0.8-2.38)	1.03(0.5-1.5)	1.16(0.52-1.42)	1.29(0.78-2.12)	1.2(0.54-2.08)
>=70	2.7(1.63-3.7)*	2.43(1.36-4.5)*	2.56(1.63-4.1)*	1.5(0.87-2.6)	3.14(1.85-5.54)*	2.5(1.35-4.5)*
Gender						
Female(ref)						
Male	1.12(0.78-1.69)*	1.6(1.03-2.7)*	2.89(2.04-4.1)*	4.7(3.125-.6)*	1.5(1.02-2.27)*	1.75(1.08-2.85)*
BMI						
Normal(ref)						
Obese	1.35(0.79-2.22)	1.29 (0.66-2.22)	0.96(0.66-2.22)	0.77(1.85-5.5)	0.82(0.48-1.42)	0.62(0.34-1.14)
Overweight	1.25(0.8-1.96)	1.26 (0.77-2.04)	1.06(0.7-1.58)	1.29(0.8-2.12)	0.8(0.49-1.29)	0.76(0.45-1.29)
Hypertension						
No(ref)						
Yse	1.2(0.54-2.2)	0.9(0.43-1.63)	1.15(0.86-2.7)	0.59(0.32-1.12)	0.84(0.47-1.42)	1.26(0.7-2.32)
High Cholesterol						
No(ref)						
Yes	1.44(1.08-1.96)*	1.28(0.72-2.27)	1.56(1.23-2)*	1.19(0.69-2.08)	1.44(1.09-1.92)*	0.65(0.33-1.29)
Diabetes						
No(ref)						
Yes	0.56(0.3-0.84)*	1.48(0.9-2.2)	0.52(0.37-0.74)	2(1.29-2.85)*	0.79(0.51-1.21)	1.09(0.68-2)
PASE						
High tertile(ref)						
Low tertile	1.05(0.66-1.65)	0.87(0.52-1.46)	1.37(0.95-1.99)	1.41(0.91-2.19)	1.94(1.19-3.18)*	1.71(0.98-2.9)
Middle tertile	0.9(0.54-1.49)	0.9(0.5-1.61)	0.65(0.4-1.05)	1.03(0.59-1.82)	1.36(0.78-2.38)	1.5(0.87-2.35)
Other medical						
Normal(ref)						
One and more	6.6(3.7-12.5)*	7.14(3.7-14.7)*	4(3.1-6.25)*	5(2.97-8.3)*	2.94(1.1-3.81)*	2.7(1.2-4.7)*
Smoking						
No(ref)						
Yes	0.735 (0.36-1.46)	1.14(0.52-2.37)	1.25(0.74-2.03)	1.16(0.66-2.05)	0.96(0.511-1.8)	1.1(0.53-2.29)

*Statistically significant, **Crude model, ***Adjusted model

While some observational studies have suggested a relationship between Vitamin D deficiency and cardiovascular events, the impact of confounding factors on these associations has not been thoroughly explored. Variables such as physical activity, dietary patterns, lifestyle choices, and overall health status could potentially confound the relationship between Vitamin D levels and cardiovascular diseases.[21] Clinical trials investigating the

effects of Vitamin D deficiency on cardiovascular disorders have yielded conflicting results. While some trials have reported an association between Vitamin D levels and cardiovascular diseases, others have failed to establish a significant link between Vitamin D levels and the risk of cardiovascular events.[5,6]

Vitamin D deficiency in the elderly population has been linked to increased oxidative stress, vascular endothelial dysfunction, and hypertension. However, our study did not find a significant association between Vitamin D levels and cardiovascular disorders, including angina, stroke, and MI. This aligns with the findings of a systematic review indicating no significant association between Vitamin D levels and the risk of cardiovascular diseases.[22] Similarly, a prospective case-control study in India found no correlation between Vitamin D levels and angina.[23] Long-term follow-up studies have also suggested that Vitamin D supplementation may not reduce the risk of MI, stroke, or cardiac-related deaths.[24] Nonetheless, in vitro studies have demonstrated that higher levels of Vitamin D may confer protective effects against cardiac injuries and hypertension.[25] Given the divergent findings in existing literature, routine screening of patients with Vitamin D deficiency for the prevention of extra-skeletal outcomes is not universally recommended. Discrepancies in defining cut-off values for Vitamin D deficiency, variations in study populations, and differences in other variables examined across studies may contribute to the inconsistencies in findings.

According to the results of the adjusted model presented in Table 2, male gender, having a medical condition, and age over 70 years were identified as risk factors for cardiovascular diseases in this study. In contrast to our findings, a large study encompassing data from six developing countries demonstrated that the age-standardized prevalence of angina was higher in women than in men, while the prevalence of stroke showed a reverse trend, consistent with our results.[26] Additionally, a study on elderly Finnish migraineurs revealed a higher risk of stroke in women compared to male participants.[27] A long-term study conducted in Iran between 2005 and 2010, involving approximately 45,000 patients, indicated that male gender was a risk factor for acute coronary syndrome, whereas stable angina was more prevalent in females.[28] Similarly, a study in Mashhad city near Neyshabur predicted a significantly higher risk of cardiovascular disease in men compared to women.[29] In alignment with our results, advanced age, male gender, and the presence of medical conditions were associated with an increased risk of stroke in the elderly population of Cuba, Havana.[30]

Regarding other significant risk factors for cardiovascular diseases such as smoking, hypertension, obesity, and diabetes, there were discrepancies between our findings and some previous studies.[31-33] Our results indicated that important predictors of cardiovascular diseases, including smoking, hypertension, diabetes, obesity, low physical activity, and high cholesterol, were not associated with an increased risk of cardiovascular diseases. The variations in findings across studies could be attributed to genetic factors, lifestyle choices, dietary habits, environmental influences, and the specific age group studied, which in our case focused on the elderly.[32,34]

It is important to acknowledge the limitations of this study. The number of key determinants included in the statistical model may have been insufficient, although efforts were made to incorporate the most relevant variables with complete data. Additionally, the data for this study were obtained from the early years of the cohort study, and future follow-ups may reveal new insights.

Conclusions

This longitudinal study highlights the high prevalence of vitamin D insufficiency and deficiency among the elderly population in Iran. Vitamin D supplementation could potentially play a beneficial role in reducing the prevalence of vitamin D deficiency and its associated health outcomes, particularly in older individuals. Our findings suggest that vitamin D deficiency is not a significant risk factor for cardiovascular diseases. However, male gender, having medical conditions (excluding hypertension and diabetes), and age over 70 years were identified as risk factors for cardiovascular diseases. Further investigations following completion of additional phases of follow-up may provide more precise and detailed information regarding the risk factors for cardiovascular diseases in the elderly.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

Coronavirus disease 2019: COVID-19;
World Health Organization: WHO

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval (code: IR.RUMS.REC.1396.119) was obtained (April 2020). The present study did not interfere with the process of diagnosis and treatment of patients and all participants signed an informed consent form.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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