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Combined 25-hydroxyvitamin D concentrations and physical activity on mortality in US stroke survivors: findings from the NHANES

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Abstract

Background 25-hydroxyvitamin D [25(OH)D] concentrations and physical activity (PA) are linked and both are associated with changes in mortality. We examined the association of 25(OH)D and PA with all-cause or cause-specific mortality risk in stroke survivors.

Methods The analysis included 677 stroke survivors from National Health and Nutrition Examination Survey (NHANES) 2007–2008 to 2017–2018. Independent and joint associations of 25(OH)D, PA and mortality among stroke survivors were analyzed using weighted Cox regression.

Results We identified 133 all-cause deaths [major adverse cardiovascular events (MACE), 34; non-MACE, 79] with a median follow-up of 5.8 years (interquartile, 2.8–8.9 years). In a range of adjusted models, high 25(OH)D was observed with lower all-cause mortality compared to low 25(OH)D (HR, 0.376; 95% CI, 0.233–0.607) and non-MACE (HR, 0.265; 95% CI, 0.143–0.490) mortality was consistently associated. At the same time, compared with no PA, PA was associated with a lower all-cause (HR, 0.280; 95%CI, 0.107–0.733) and non-MACE (HR, 0.266; 95%CI, 0.087–0.810) was associated with a lower risk of death. In addition, pooled analyses showed that stroke survivors with high 25(OH)D and PA had the lowest risk of all-cause death (HR, 0.132; 95%CI, 0.038–0.460) and non-MACE (HR, 0.092; 95%CI, 0.023–0.363), there is an additive interaction between 25(OH)D and PA in non-MACE.

Conclusion In conclusion, this study found that combining high 25(OH)D levels and PA showed an enhanced protective effect which demonstrated a synergistic effect between them in reducing mortality among stroke

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survivors. These findings provide new ideas and possibilities for the prevention and treatment of cardiovascular and cerebrovascular diseases, offering a reference for development of clinical practice guidelines in the future.

Keywords 25-hydroxyvitamin D, Physical activity, Mortality, Stroke survivors

Introduction

Stroke is the second leading cause of death, the third leading cause of disability and the leading cause of dementia globally [1, 2]. Due to population growth and ageing, the absolute number of global deaths from stroke will increase by 50% from 2020 to 9.7 million in 2050. The burden from stroke will continue to increase worldwide [3]. Therefore, effective stroke prevention and post-stroke management programs are essential, including early detection and control of risk factors such as hypertension, dyslipidemia, obesity and diabetes. Lifestyle interventions such as regular physical activity (PA) are also important [4].

Vitamin D is a fat-soluble vitamin with functions such as promoting calcium and phosphorus absorption, regulating cell growth and differentiation and modulating immunity. Previous scientific studies have shown that low vitamin D levels are closely related to cardiovascular diseases [5] and are associated with the occurrence and progression of stroke [6–12]. However, other studies have shown that despite the improvement in vitamin D status, there is no significant difference in the incidence of cardiovascular and cerebrovascular events and mortality between the use of vitamin D supplements and placebo [13, 14]. Also, there was no significant effect on functional outcome of stroke patients [15]. 25-hydroxyvitamin D [25(OH)D] is an important indicator for assessing and detecting vitamin D deficiency. In recent years, a number of investigations have found that serum 25(OH)D concentration has a nonlinear relationship with mortality in the general population. A meta-analysis found that the reduction in mortality may not be significant in individuals with an increase of 87.5 nmol/L in 25(OH)D compared to individuals with an increase of 12.5, 25, and 50 nmol/L in 25(OH)D [16]. This phenomenon may be caused by calcification of blood vessels caused by excessive vitamin D [17]. Lower serum 25(OH)D concentrations significantly correlate with heightened stroke risk, clinical severity, and unfavorable prognosis in stroke patients [18, 19].

The health benefits of PA as one of the modifiable risk factors for stroke need no elaboration [20]. A systematic review and meta-analysis found that PA of any level and intensity was associated with a significant reduction in the risk of all-cause deaths. The greatest risk reductions occurred at light- or moderate-intensity PA [21]. For stroke patients, pre-stroke PA contributes to stroke risk reduction and may be associated with reduced stroke severity [22–24]. At the same time, regular PA and moderate sunlight exposure is a simple and feasible method to prevent and treat vitamin D deficiency [25]. Vitamin D can be produced in human epidermis by ultraviolet radiation from sunlight and then converted in the liver into 25(OH)D [26]. In addition to increasing sunlight exposure, the effects of physical activity on vitamin D May be related to its role in bone health but the specific mechanisms have not been elucidated [27]. Multiple studies have shown that increased PA can increase 25(OH)D levels [28–30]. Thus, we identified a research gap: the lack of studies exploring the combined effects of PA and vitamin D status on stroke patients. In this study, we hypothesised that vitamin D status and PA have a synergistic effect on reducing mortality of stroke patients.

To fill this gap, we aimed to independently and jointly examine the association of adult serum 25(OH)D concentrations and PA with mortality among stroke survivors in the US population using data from samples from the National Health and Nutrition Examination Survey (NHANES) database.

Methods

This prospective cohort study used a nationally representative sample from the NHANES of the National Center for Health Statistics (NCHS). The survey consisted of questionnaire interviews, laboratory tests and physical examinations. The NHANES study protocol was approved by the NCHS Ethics Review Board and written informed consent was obtained from all participants.

Study population

Firstly, participants were asked, 'Has a doctor or other health professional ever told you that you had a stroke?' If the participant answered 'yes', they were defined as stroke survivors. Data from participants who took part in six NHANES from 2007 to 2008 to 2017–2018 were further linked to their mortality outcomes. Of these participants ($n = 1398$), individuals with missing 25(OH)D data ($n = 194$), age > 70 years ($n = 525$), and lack of mortality data ($n = 2$) were excluded from analyses. A total of 677 patients were included in the final analysis (Fig. 1).

Assessment of mortality

The primary outcome of the study was all-cause mortality and the secondary outcomes were major adverse cardiovascular events (MACE, which includes deaths from heart disease and cerebrovascular disease) and non-MACE. Death from all reasons was defined as all-cause mortality and MACE was defined as ICD-10 codes

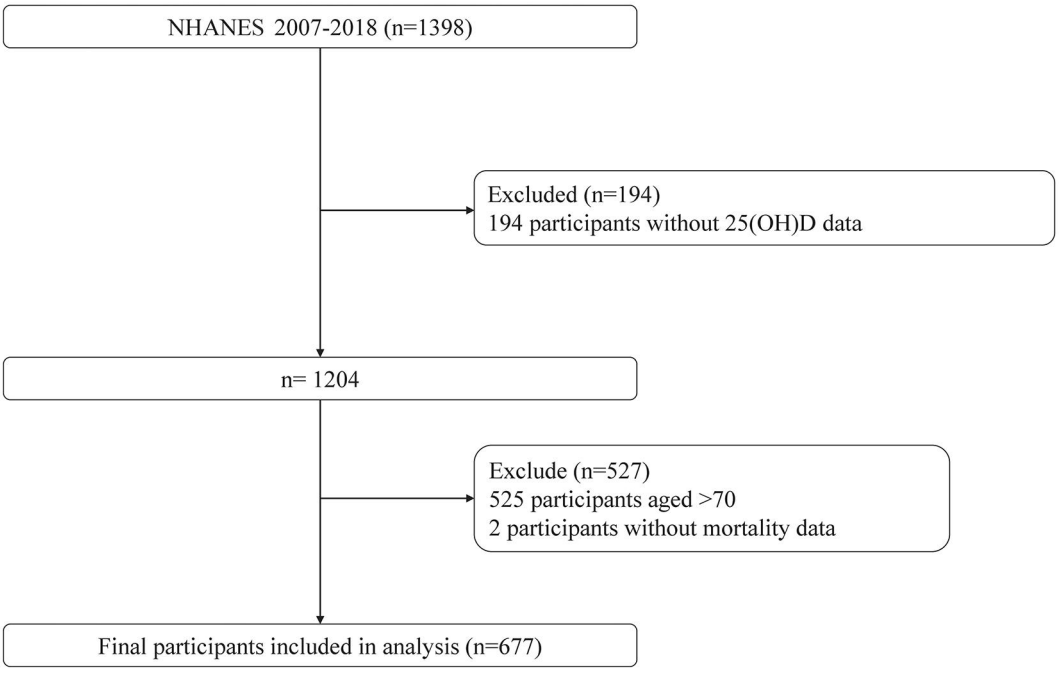

Fig. 1 Flow chart for subject selection

I60-I69, I00-I09, I11, I13 and I20-I51. If the death does not meet MACE, it is defined as non-MACE. The follow-up period of the study was from the initial diagnosis to the date of death or the end of the study period (31 December 2019), whichever comes first.

Measurement of PA patterns

PA was assessed using weekly PA participation information collected using the Global Physical Activity Questionnaire created by the World Health Organisation. PA data were converted to metabolic equivalent minutes of moderate to vigorous PA (MET) per week. Respondents were categorized according to whether they met the criteria for MET (≥ 600 MET minutes/week, equivalent to 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity PA) or did not meet the recommended guidelines for adults (< 600 MET minutes/week).

Assessment of covariates

All-cause mortality, MACE and non-MACE analyses considered the same set of covariates. Participant characteristics included age, gender, race, education level, history of smoking and drinking, body mass index (BMI), diabetes, hypertension, dyslipidemia, and history of cardiovascular disease (CVD). Race was categorized as non-Hispanic white, non-Hispanic black, Mexican American, Other Hispanic, and other. Education was categorized as Less Than 12th Grade, High School Grade or Equivalent, Some College, or College Graduate or above. Smoking was categorized as never smoker, former smoker and current smoker. Drinking was categorized as lifetime abstainer, former drink and current drink. BMI was calculated as weight in kilograms divided by the square of height in meters and was classified as normal (< 25.0 kg/m2), overweight (25.0 to 30 kg/m2), and obese (≥ 30.0 kg/m2). Diabetes, CVD and hypertension is diagnosed by self-report.

Statistical analysis

Appropriate sampling weights were used in analyses to account for the complex NHANES survey design, in accordance with NHANES analysis guidelines. Continuous variables were expressed as mean ± standard error (SE), and one-way ANOVA was used for between-group comparisons. Data for categorical variables were expressed as numbers (%) and comparisons between groups were made using the Rao-Scott Chi-square method. Multivariate Cox proportional risk regression models were applied to hazard ratio (HR) and 95% CI for the associations between 25(OH)D and/or PA and overall mortality, MACE, and non-MACE, respectively. HR is the ratio of morbidity or mortality in the exposed group to that in the non-exposed group at a specific time [31]. Restricted cubic spline (RCS) curve and Cox proportional risk models were used to depict the nonlinear association between 25(OH)D and all-cause mortality. In addition to the main Cox proportional risk regression model, an interaction term was introduced to assess whether the combined effects of 25(OH)D and PA status outweighed the cumulative effect of both on additive and

Table 1 Baseline characteristics of US stroke survivors according to the PA status

Characteristic	All	No PA	PA	
Overall	677	556	121	
Gender (%)				< 0.001
Male	324(47.9)	248(44.6)	76(62.8)	
Female	353(52.1)	308(55.4)	45(37.2)	
Age	57.2(10.6)	57.5(9.9)	55.8(13.3)	0.107
Race (%)				0.222
Mexican American	81(12.0)	64(11.5)	17(14.0)	
Other Hispanic	55(8.1)	49(8.8)	6(5.0)	
Non-Hispanic White	257(38.0)	211(37.9)	46(38.0)	
Non-Hispanic Black	223(32.9)	187(33.6)	36(29.8)	
Other Race	61(9.0)	45(8.1)	16(13.2)	
Weight status, BMI (%)				0.008
< 25	147(21.7)	112(20.1)	35(28.9)	
25 to < 30	193(28.5)	152(27.3)	41(33.9)	
≥ 30	337(49.8)	292(52.5)	45(37.2)	
Educational levels (%)				< 0.001
Less Than 12th Grade	212(31.3)	188(33.8)	24(19.8)	
High School Grade or Equivalent	194(28.7)	160(28.8)	34(28.1)	
Some College	191(28.2)	159(28.6)	32(26.4)	
College Graduate or above	80(11.8)	49(8.8)	31(25.6)	
Smoking status (%)				0.006
Never smoker	224 (36.0)	195(35.1)	49(40.5)	
Former smoker	193(28.5)	149(26.8)	44(36.4)	
Current smoker	240(35.5)	212(38.1)	28(23.1)	
Drinking status (%)				0.071
Lifetime abstainer	69(10.2)	53(9.5)	16(13.2)	
Former drink	90(13.3)	81(14.6)	9(7.4)	
Current drink	518(76.5)	422(75.9)	96(79.3)	
Diabetes (%)	219(32.3)	193(34.7)	26(21.5)	0.007
Dyslipidemia (%)	389(57.5)	332(59.7)	57(47.1)	0.015
Hypertension (%)	507(74.9)	424(76.3)	83(68.6)	0.100
History of CVD (%)	566(83.6)	464(83.5)	102(84.3)	0.927
25(OH)D	59.2(29.9)	58.8(30.2)	61.3(28.6)	0.404

Abbreviations PA, physical activity; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; 25(OH)D, 25-hydroxyvitamin D

multiplicative scales. Specifically, we calculated relative excess risk (RERI) to assess additive scale interactions [32]. For the multiplicative scales, we added a cross-product term between 25(OH)D and PA status in the multivariate Cox model to test for multiplicative interactions. Survival analyses were performed using the Kaplan-Meier method, in which the probability of survival in the population was assessed according to the PA status and 25(OH)D concentrations and compared using the log-rank test. Finally, stratified analyses were performed to test the stability of our results. Missing data were replaced by multiple interpolations. Multiple interpolation was performed in R with a software package called "Mice" (Buuren and Groothuis-Oudshoorn, 2011). All

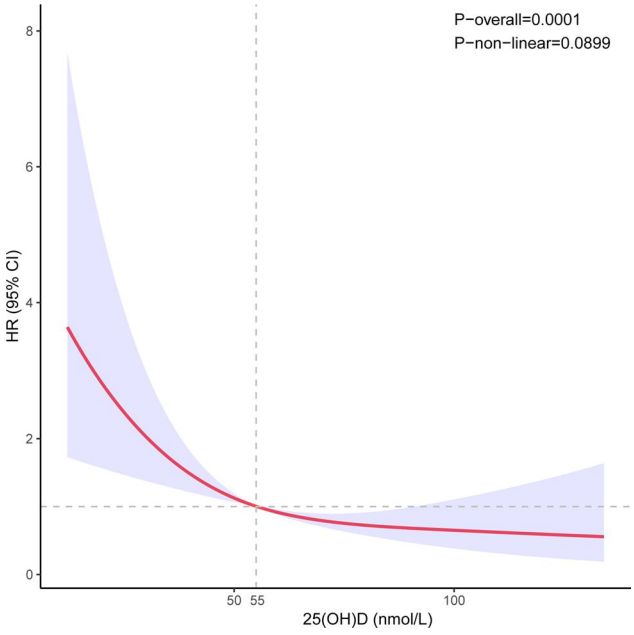

Fig. 2 Association of 25(OH)D levels with all-cause mortality among US stroke survivors by Restricted Cubic Splines. HR, Hazard ratios

tests were two-sided, and a P value of 0.05 was considered statistically significant. All analyses were performed by the R Statistical Program (http://www.R-project.org, R Foundation), Free Statistics Analysis Platform, and Statistical Package for the Social Sciences 25.0.

Result

Baseline characteristics

A total of 677 stroke survivors were recruited (weighted population, 3677570; age = 57.2 ± 10.6 years (mean ± SE); 47.9% male). Table 1 shows the characteristics of the participants by PA status. Patients were divided into two groups based on patient PA status: without PA ($n = 556$) and with PA ($n = 121$). Participants with PA appeared to be more likely to be male, be better educated, have a lower body mass index (BMI), be less likely to smoke, and have a lower prevalence of diabetes and dyslipidemia.

Association between PA status or 25(OH)D concentrations and mortality

With a median follow-up period of 5.8 years (interquartile range, 2.8–8.9 years), 113 of the 677 patients died, with 34 of MACE and 79 of non-MACE. The RCS curve showed an L-shaped relationship between 25(OH)D and all-cause mortality, with a point of infection of approximately 55 nmol/L (Fig. 2). Based on this point of infection, 25(OH)D was divided into low and high concentration groups. In independent analyses, weighted COX proportional risk model suggested that 25(OH)D and PA were negatively associated with all-cause mortality and non-MACE, while no similar correlation was

observed in MACE (Table 2). Specifically, after adjusting for covariates, the HR for all-cause mortality, MACE and non-MACE were 0.376 (95% CI, 0.233–0.607), 0.934 (95% CI, 0.383–2.281) and 0.265 (95% CI, 0.143–0.490) respectively in individuals with a high 25(OH)D level compared with those with a low level of 25(OH)D. Patients with PA had lower all-cause mortality (HR,0.280;95% CI, 0.107–0.733) and non-MACE (HR,0.266;95% CI, 0.087–0.810) than patients with No PA.

Joint association of 25(OH)D levels and PA status with mortality

In the combined analysis, patients with vitamin D deficiency and PA insufficiency had the highest risk of all-cause mortality and non-MACE (Fig. 3). Compared with the combination of vitamin D deficiency and PA insufficiency, the HR for all-cause death and non-MACE in the vitamin D deficiency and PA groups were 0.132 (95% CI, 0.038–0.460),0.092(0.023,0.363) (Table 3). In addition, we performed an interaction test to analyse the interaction between 25(OH)D levels and PA and death. We found an additive effect between 25(OH)D levels and PA in non-MACE stroke survivors (estimate 0.549; 95% CI 0.215, 0.883), but no multiplicative or additive effects were found for all-cause mortality and MACE (Table 4). The Kaplan–Meier curves for all-cause mortality and non-MACE also showed that vitamin D deficiency and PA insufficiency had the lowest survival rates (Fig. 4).

Stratified analyses

Stratified analyses were performed according to age, sex, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption and body mass index (Fig. 5). The results showed that higher 25(OH)D levels were associated with lower mortality among men, hypertensive, dyslipidemia, BMI < 25, current smokers and alcohol drinkers. On the other hand, PA was more strongly associated with lower mortality among those who were non-diabetic, hypertensive, dyslipidemia, body mass index < 25 and current alcohol drinkers. No interaction was found in all subgroups.

Discussion

In this prospective study, we found that moderate-intensity PA and high 25(OH)D levels (> 55 nmol/L) reduced the risk of all-cause mortality and non-MACE while no similar correlation was observed in MACE in stroke survivors aged 70 years and younger. Moreover, there was an interaction between serum 25(OH)D levels and PA status. When combined, they can significantly enhance the protective effect. Patients with higher 25(OH)D levels

Table 2 Association of PA and 25(OH)D with mortality in US stroke survivors aged 70 years and younger, NHANES, 2007 to 2018

Mortality outcome	Adjusted model 1	*P* value	Adjusted model 2	*P* value	Adjusted model 3	*P* value
	HR (95%CI)		HR (95%CI)		HR (95%CI)	
All causes						
25(OH)D	0.988(0.977,0.999)	0.026	0.984(0.975,0.994)	0.001	0.984(0.974,0.993)	0.001
25(OH)D						
Lower	1 (Ref)		1(Ref)		1(Ref)	
Higher	0.466(0.279,0.779)	0.004	0.392(0.248,0.617)	< 0.001	0.376(0.233,0.607)	< 0.001
PA						
No	1 (Ref)		1(Ref)		1(Ref)	
Yes	0.242(0.098,0.594)	0.002	0.280(0.106,0.738)	0.010	0.280(0.107,0.733)	0.01
MACE						
25(OH)D	0.998(0.981,1.015)	0.799	0.998(0.983,1.013)	0.750	1.000(0.984,1.016)	0.989
25(OH)D						
Lower	1 (Ref)		1(Ref)		1(Ref)	
Higher	0.773(0.316,1.889)	0.573	0.794(0.315,2.000)	0.624	0.934(0.383,2.281)	0.882
PA						
No	1 (Ref)		1(Ref)		1(Ref)	
Yes	0.187(0.038,0.922)	0.039	0.312(0.062,1.571)	0.158	0.309(0.063,1.527)	0.150
Non-MACE						
25(OH)D	0.983(0.970,0.997)	0.017	0.978(0.966,0.991)	< 0.001	0.977(0.965,0.988)	< 0.001
25(OH)D						
Lower	1 (Ref)		1(Ref)		1(Ref)	
Higher	0.383(0.202,0.727)	0.003	0.295(0.168,0.518)	< 0.001	0.265(0.143,0.490)	< 0.001
PA						
No	1 (Ref)		1(Ref)		1(Ref)	
Yes	0.268(0.093,0.768)	0.014	0.262(0.083,0.828)	0.023	0.266(0.087,0.810)	0.02

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, race, body mass index, education, history of smoking and drinking. Model 3 adjusted for age, sex, race, body mass index, education, history of smoking and drinking, and health factors (hypertension, dyslipidemia, diabetes, CVD)

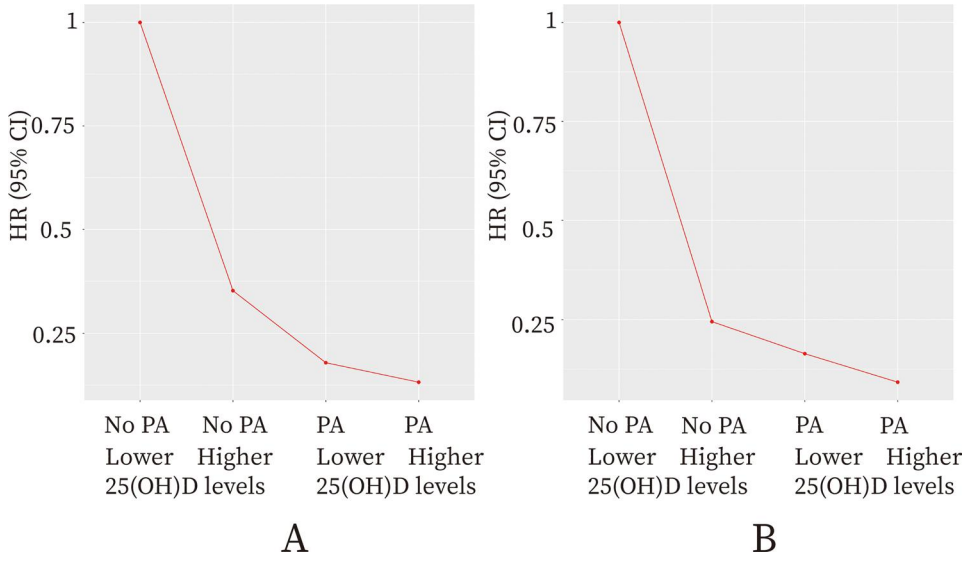

Fig. 3 Joint association of 25(OH)D levels and PA status with mortality among US stroke survivors. **A**, all-cause mortality; **B**, non-MACE

Table 3 Joint association of PA and 25(OH)D with mortality in US Stroke survivors aged 70 years and younger, NHANES, 2007 to 2018

Mortality outcome	NLR	Adjusted model 1	*P* value	Adjusted model 2	*P* value	Adjusted model 3	*P* value
		HR (95%CI)		HR (95%CI)		HR (95%CI)	
All causes							
25(OH)D lower	No PA	1(Ref)		1(Ref)		1(Ref)	
	PA	0.447(0.263,0.760)	0.003	0.375(0.229,0.616)	< 0.001	0.353(0.210,0.592)	< 0.001
25(OH)D higher	No PA	0.152(0.063,0.364)	< 0.001	0.190(0.078,0.463)	< 0.001	0.179(0.072,0.444)	< 0.001
	PA	0.154(0.050,0.473)	0.001	0.142(0.040,0.508)	0.003	0.132(0.038,0.460)	0.001
MACE							
25(OH)D lower	No PA	1(Ref)		1(Ref)		1(Ref)	
	PA	0.750(0.304,1.848)	0.531	0.765(0.278,2.102)	0.603	0.902(0.336,2.417)	0.837
25(OH)D higher	No PA	0.131 (0.025,0.690)	0.017	0.229(0.046,1.132)	0.071	0.246(0.052,1.167)	0.078
	PA	0.169(0.021,1.346)	0.093	0.282(0.029,2.792)	0.279	0.313(0.035,2.785)	0.297
Non-MACE							
25(OH)D lower	No PA	1(Ref)		1(Ref)		1(Ref)	
	PA	0.363(0.178,0.740)	0.005	0.284(0.149,0.541)	< 0.001	0.245(0.124,0.484)	< 0.001
25(OH)D higher	No PA	0.163(0.062,0.426)	< 0.001	0.178(0.060,0.532)	0.002	0.164(0.055,0.488)	0.001
	PA	0.152(0.040,0.578)	0.006	0.107(0.024,0.467)	0.003	0.092(0.023,0.363)	< 0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, race, body mass index, education, history of smoking and drinking. Model 3 adjusted for age, sex, race, body mass index, education, history of smoking and drinking, and health factors (hypertension, dyslipidemia, diabetes, CVD)

Table 4 Interaction analysis of 25(OH)D levels and PA status with mortality in US stroke survivors aged 70 years and younger, NHANES, 2007 to 2018

Additive interaction (RERI)				Multiplicative interactive	*P* value
Mortality outcome	Estimate	Lower	Upper	HR (95%CI)	
All causes	0.341	-0.034	0.716	2.092(0.461,9.485)	0.339
MACE	-0.576	-2.058	0.905	1.408(0.075,26.603)	0.819
Non-MACE	0.549	0.215	0.883	2.285(0.442,11.824)	0.342

and PA status had the lowest risk of all-cause mortality and MACE. Additionally, we found an additive effect between 25(OH)D and PA in non-MACE stroke survivors. But no multiplicative or additive effects were found for all-cause mortality and MACE. The significance of these correlations remained even after multiple adjustments of traditional risk factors such as body mass index, education, history of smoking and drinking, and health factors (hypertension, dyslipidemia, diabetes, CVD). As far as we know, this is the first study to evaluate the combined influence of 25(OH)D levels and PA status on mortality risk among stroke survivors.

Vitamin D has a protective effect on ischemic stroke. Low concentration of 25(OH)D may increase the risk of stroke occurrence and is positively correlated with unfavourable short-term and long-term prognosis of stroke [8–10]. Accordingly, vitamin D supplementation has a positive effect on functional recovery after stroke which

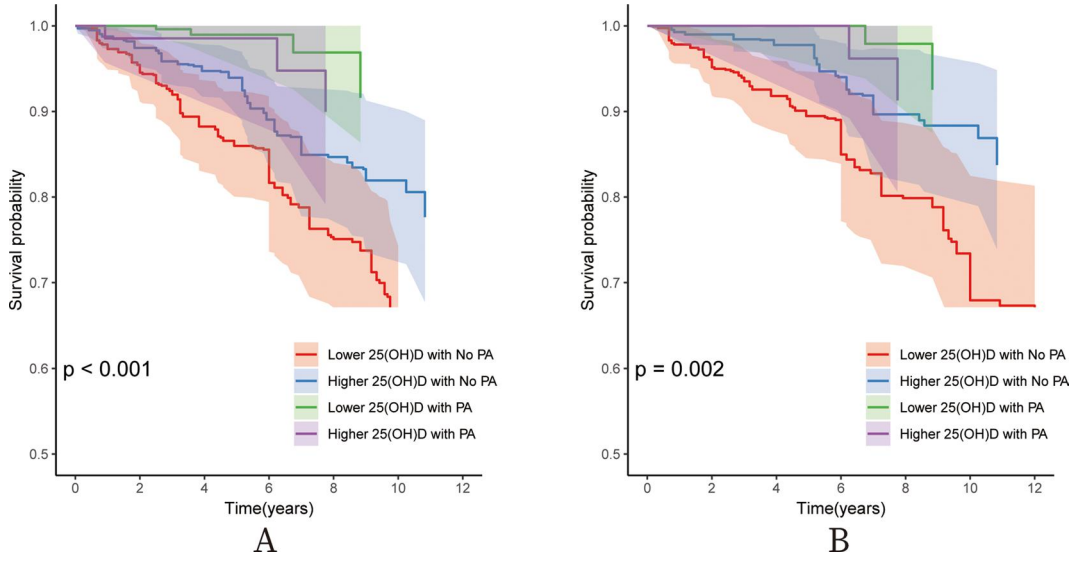

Fig. 4 Kaplan-Meier curves for the relationship between 25(OH)D levels, PA status and all-cause mortality and non-MACE. **A**, all-cause mortality; **B**, non-MACE

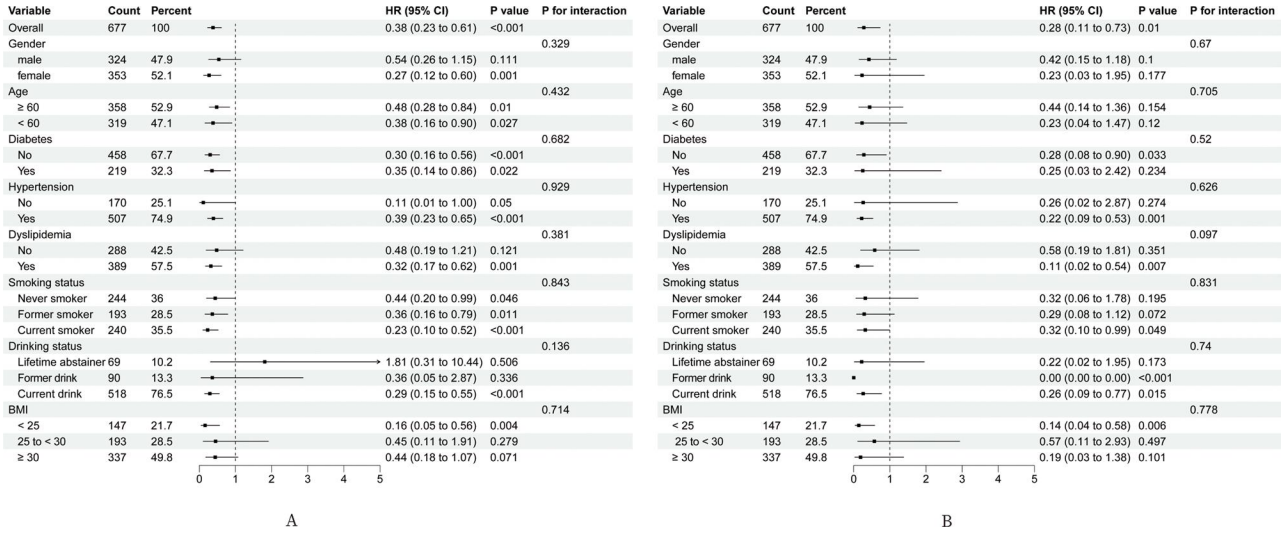

Fig. 5 Stratified analysis of association between 25(OH)D levels and PA status and all-cause mortality. **A**, 25(OH)D levels and all-cause mortality; **B**, PA status and all-cause mortality. Models were adjusted for age, sex, race, body mass index, education, history of smoking and drinking, and health factors (hypertension, dyslipidemia, diabetes, CVD)

can reduce the mortality of stroke survivors, brain injury and inflammatory response and promote angiogenesis and neuroprotection [11, 12, 33]. Among them, vitamin D3 can interfere with the key molecular mechanisms of neuronal death and survival at each stage of stroke. It has various effects such as neuroprotection, anti-oxidation, anti-inflammation, regeneration and anti-aging which helps to restore the reperfusion of cerebrovascular area, recover the normal function of blood brain barrier and reduce the volume of cerebral infarction [34, 35]. Vitamin D deficiency leads to vascular endothelial dysfunction and thickened blood vessel wall which in turn affects the normal function of cerebral blood vessels and increases the risk of stroke and cognitive impairment [36]. Therefore, patients with vitamin D deficiency have lower survival rates after stroke and are more likely to have recurrent stroke or death while vitamin D supplementation can help stroke recovery [37, 38]. However, an observational analysis and a modified Mendelian randomization analysis showed an association, but not a causal relationship, between higher 25(OH)D concentration levels and lower risks for coronary heart disease and stroke as well as all-cause death. This suggests that interventions like increasing 25(OH)D concentrations (i.e., vitamin D supplementation) are unlikely to cause a significant reduction in cardiovascular disease or

all-cause mortality in the overall population [39]. Due to the large heterogeneity of current clinical studies including inconsistencies in research design, evaluation indicators and conclusions, vitamin D supplementation is not recommended for stroke prevention or treatment in individuals without vitamin D deficiency. However, as for people with 25(OH)D deficiency, rational use of vitamin D therapy may still remain to be a potential prevention and treatment for ischemic stroke [6].

There is no doubt that regular PA contributes to health. It can reduce or delay the occurrence of cardiovascular disease, cerebrovascular accidents, type 2 diabetes, and certain types of cancer as well as enhanced cognitive function and mental health [20, 40]. The WHO recommends 150 to 300 min of moderate-intensity PA or 75 to 150 min of vigorous-intensity PA per week for each adult [20]. Pre-stroke PA is associated with milder stroke and better functional outcome. The higher the pre-stroke PA levels, the better the post-stroke functional outcome, reflected as higher levels of vascular endothelial growth factor expression, fewer complications, reduced infarct growth and smaller final infarct volume [41–43]. The disabling characteristic of stroke leads to the inevitable limitation of PA in stroke survivors after onset. PA levels after stroke are very low and data on PA levels during the acute phase after stroke are quite limited [44]. A study in patients with minor ischemic stroke showed that reducing sedentary behavior and increasing light intensity PA after discharge reduced the risk of stroke recurrence [45]. Another study showed that locomotor and balance trainings and aerobic exercise interventions improved mobility and cognition in chronic stroke survivors [46]. At the same time, the study also found that an increase in medium intensity PA can directly affect increasing 25(OH)D concentration by reducing body weight and fat percentage [28]. Together, they reduced the risk of death in stroke survivors aged 70 years and younger. This may explain our finding of an additive interaction between high 25(OH)D and PA in non-MACE stroke survivors.

The strength of our study is the use of a nationally representative sample of US stroke survivors. It means that our findings can be better generalized to other populations and allows us to perform well-controlled analyses while accounting for various confounders. Of course, we have some limitations. First, our study used a single measurement of 25(OH)D levels and did not consider the long-term changes in 25(OH)D. Second, the study relied on self-reported data on PA and did not objectively assess the intensity of PA through quantifiable methods. It was difficult to avoid possible problems such as memory bias and information distortion. Finally, although we controlled for many possible confounding factors, the findings may also be influenced by other confounding factors affecting post-stroke mortality.

Conclusion

In conclusion, this study found that adequate 25(OH) D levels (> 55 nmol/L) and participation in moderate intensity of PA were associated with lower mortality in stroke survivors. Furthermore, combining high 25(OH) D levels and PA showed an enhanced protective effect which demonstrated a synergistic effect between them in reducing mortality among stroke survivors. These findings provide new ideas and possibilities for the prevention and treatment of cardiovascular and cerebrovascular diseases, offering a reference for development of clinical practice guidelines in the future.

Abbreviations

MACE	Major adverse cardiovascular events
PA	Physical activity
NHANES	National Health and Nutrition Examination Survey
25 (OH) D	25-hydroxyvitamin D
BMI	Body mass index
CVD	Cardiovascular disease
RCS	Restricted cubic spline
SE	Standard error
95% CI	95% Confidence interval
HR	Hazard ratios

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Author contributions

Minghua Wu and Junqi Liao conceived the protocol, Junqi Liao, Jingyi chen, Yuan Zhu and Wenlei Li contributed to analysis and interpretation of data. Junqi Liao and Jingyi chen grafted the manuscript. Huimin Wu, Qing Zhu, Xiaogang Tang, Li Li, Aimei Zhang, Peiyi Mo, Yan Liu, Xinyi Yang, Yang Han and Zhaoyao Chen critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. The corresponding author had full access to all data in the study and assumed final responsibility for the decision to submit the manuscript for publication.

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Data availability

The datasets generated for this study are available on request to the corresponding author.

Declarations

Competing interests

The authors declare no competing interests.

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