25(OH)D deficiency is associated with fatal stroke among whites but not blacks: The NHANES-III linked mortality files

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Abstract

Objective—Deficient 25-hydroxyvitamin D [25(OH)D] levels are associated with cardiovascular disease (CVD) events and mortality. Both 25(OH)D deficiency and stroke are more prevalent among blacks. We examined whether low 25(OH)D contributes to the excess risk of fatal stroke in blacks compared to whites.

Research Methods and Procedures—The Third National Health and Nutrition Examination Survey, a probability sample of US civilians, measured 25(OH)D levels and CVD risk factors between 1988–1994. Vital status through December 2006 was obtained via linkage with the National Death Index. Among white and black adults without CVD reported at baseline (n=7981), Cox regression models were fit to estimate hazard ratios (HR) for fatal stroke by 25(OH)D status and race.

Results—During a median of 14.1 years, there were 116 and 60 fatal strokes among whites and blacks respectively. The risk of fatal stroke was greater in blacks compared to whites in models adjusted for socio-economic status and CVD risk factors, [HR 1.60 (95% CI 1.01–2.53)]. Mean baseline 25(OH)D levels were significantly lower in blacks compared to whites (19.4 vs 30.8 ng/mL, respectively). In multivariable-adjusted models, deficient 25(OH)D levels <15 ng/mL were associated with fatal stroke among whites [HR 2.13 (1.01–4.50)] but not blacks [HR 0.93 (0.49–1.80)].

Conclusions—Vitamin D deficiency was associated with increased risk of stroke death in whites but not blacks. Although blacks had a higher rate of fatal stroke compared to whites, the

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low 25(OH)D levels in blacks were unrelated to stroke incidence and therefore 25(OH)D levels did not explain this excess risk.

Keywords

vitamin D; stroke; racial differences

Introduction

Vitamin D has long been known to be vital to bone health. More recently, low 25-hydroxyvitamin D [25(OH)D] levels have been associated with incident cardiovascular disease (CVD) events[1] including stroke[2,3] and all-cause mortality[4] - associations that remain even after traditional risk factors and lifestyle factors are taken into account.[5]

25(OH)D is widely viewed as the superior biomarker for assessing vitamin D status, since in the serum the active form, $1,25(OH)_2D$, is not reflective of body stores as it is tightly regulated by serum calcium, phosphate, and parathyroid hormone (PTH).[6] While there is no absolute consensus regarding optimal 25(OH)D levels, levels >30 ng/ml, a threshold associated with maximal suppression of PTH and reduced fractures,[7] are generally considered sufficient. However, a recent update by the Institute of Medicine considered 25(OH)D levels >20 ng/ml as adequate.[8]

25(OH)D levels vary based on season, geographic location, and race/ethnicity, with 80% of black adults living in the United States (US) estimated to have insufficient levels <30 ng/ml. [9] Several explanations may account for lower 25(OH)D among blacks including increased cutaneous melanin which reduces UVB-synthesis of vitamin D, lower dietary consumption of vitamin D-fortified foods,[10,11] and racial differences in vitamin D metabolism.[12] A recent systematic literature review confirmed that ethnic minorities had significantly higher rates of both 25(OH)D insufficiency and obesity-related chronic diseases compared to whites.[13] However, because most of the studies were cross-sectional, temporality of the relation between vitamin D insufficiency and its association with type 2 diabetes, the metabolic syndrome, and CVD among minorities is unclear [13]. Prospective data regarding CVD outcomes by vitamin D status is needed for minorities, especially those with darker skin pigmentation.

Stroke is the third leading cause of death in the US and a leading cause of disability.[14] Blacks have more than twice the risk of stroke compared to whites at every age with the greatest racial differences seen among those aged <65 years.[15] While some of the racial disparity in stroke is attributed to factors related to socioeconomic status and traditional risk factors, residual excess risk for stroke among blacks remains after accounting for these factors.[16]

Potentially, 25(OH)D deficiency, a condition that can easily be screened for and treated, may in part explain the excess risk of stroke among blacks, perhaps mediated through vitamin D's influences on inflammation, hypertension, and diabetes risk.[5] Previous work suggested that racial differences in 25(OH)D explain approximately one-third of the excess risk of peripheral arterial disease,[17] two-thirds of the excess risk of end-stage renal disease,[18] and half of the increased hypertension prevalence in blacks compared with whites.[19] Using data from the third National Health and Nutrition Examination Survey (NHANES-III) linked to mortality files, we evaluated the association of 25(OH)D with risk of fatal stroke among white and black adults. We also sought to determine whether racial differences in 25(OH)D levels contribute to the excess risk of stroke mortality among blacks.

Materials and Methods

Study Participants

NHANES-III is a nationwide probability sample of non-institutionalized US civilian persons conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) between 1988–1994.[20] Data collection occurred during a home interview and a health examination conducted in a mobile examination clinic. Northern states were surveyed during the summer, and southern states were surveyed during the winter.[20] Non-Hispanic blacks and the elderly were over-sampled in NHANES-III. The NHANES-III protocols were approved by the institutional review boards of NCHS and CDC. Informed consent was obtained from all participants.

A total of 13,065 persons aged ≥30 years completed a physical exam as part of NHANES-III. We excluded those with a self-reported race/ethnicity other than white or black (n=3653), those with a history of previous stroke or clinical CVD (n=1050), those with missing information on 25(OH)D status (n=373), and those who did not provide sufficient personal identifying information in order to be eligible for vital status follow-up (n=8). The remaining 7981 adults (5001 white, 2980 black) were eligible for mortality follow-up.

Baseline Study Variables

Interview questions (including ascertainment of demographics and lifestyle factors), physical examination, and laboratory values (including cholesterol, C-reactive protein (CRP), and creatinine) were assessed in all study participants during 1988–1994 and processed per standard protocol as further described in the NHANES-III operating manual. [20]

The frequency and duration of moderate to vigorous intensity leisure-time physical activities performed for at least 10 minutes at a time during the past month was determined by questionnaire. Hypertension was defined by an average systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, physician diagnosis, or medication use. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Hypercholesterolemia was defined as a total cholesterol ≥240 mg/dL or medication use. Diabetes was defined by history (for women, non-gestational diabetes), use of diabetes medications, fasting glucose ≥126 mg/dL or non-fasting glucose ≥200 mg/dL. Glomerular filtration rate (GFR) was estimated with the Modification of Diet in Renal Disease Study equation.[21]

25(OH)D was measured using the Diasorin radioimmunoassay (RIA) kit (Stillwater, MN) on frozen serum between 1994–1995. Total coefficients of variations (CV%) from quality control samples were 13–19%. The RIA kit was calibrated using HPLC-purified 25(OH)D every 6 months.

Assessment of Fatal Stroke

Mortality outcomes were collected through December 31, 2006 using probabilistic matching, with up to 12 identifying data elements, to National Death Index records and were made available in early 2010. A selected sample of death certificates was reviewed manually to validate the process. The underlying cause of death was coded according to the 9th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-9) for deaths occurring between 1988–1998, and by the 10th revision (ICD-10) for 1999–2006. All deaths coded by ICD-9 were re-coded into comparable groups based on the ICD-10 underlying cause of death. For this analysis, "fatal stroke" included deaths coded as due to cerebrovascular disease (ICD-10 codes I60–I69).

Statistical analyses

All analyses were weighted to the US population to provide nationally representative estimates. SAS-callable SUDAAN statistical software, version 9.0 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the complex survey design. Differences in sample characteristics according to race and quartiles of 25(OH)D were determined with independent sample t-tests for continuous and χ^2 tests for categorical measures.

We computed length of follow-up as the time elapsed from the health examination to the date of death for decedents and December 31, 2006 for survivors. Multivariable Cox regression models were fit to estimate the hazard ratios (HR) for fatal stroke by 25(OH)D and race. For this analysis, 25(OH)D levels <15 ng/ml were considered to be "deficient" as this is the threshold previously noted to be associated with increased risk of CVD events and mortality with no statistically significant increased CVD risk noted in the "insufficient" range of 15–30 ng/ml (i.e. a non-linear association).[1,4]

Covariates in the multivariable models were selected *a priori* based on published potential confounders of the relationship between 25(OH)D and CVD. Three sequential multivariable models were explored. The first model adjusted for age and sex, while the second adjusted additionally for season of examination, lifestyle (i.e. BMI, current smoking, alcohol use, physical activity) and socioeconomic factors (i.e. income, education). The third model additionally adjusted for potential mediators in the suspected causal pathway between 25(OH)D and stroke, including diabetes, hypertension, hypercholesterolemia, and CRP.

Statistical significance was defined at the *p*<0.05 level using two-sided tests for the primary models. Effect modification (i.e. interaction testing) was evaluated with the Wald test.

Results

During a median of 14.1 years follow-up, there were 176 cases of fatal stroke (N=116 among whites, N=60 among blacks). The stroke rate was higher in blacks compared to whites (1.08 vs 0.90 per 1000 person-years, respectively) [Table 1]. Baseline characteristics of the study population by race and by subsequent development of fatal stroke are outlined in Table 1. Among both races, those who experienced a fatal stroke were older on average, had lower incomes, lower GFRs, and more traditional CVD risk factors such as hypertension and hypercholesterolemia.

The race-stratified clinical characteristics of the study population by race-specific quartiles of 25(OH)D levels are described in Table 2. Among whites, on average, those with lower 25(OH)D levels were older, more often female, less physically active, and had higher BMIs, CRP levels, and more traditional CVD risk factors (diabetes, hypertension, and hypercholesterolemia). Among blacks, those with lower 25(OH)D levels were younger and actually had higher GFRs and less hypertension and hypercholesterolemia. Other associations (sex, BMI, physical activity, CRP) were similar to whites.

Mean 25(OH)D levels were significantly lower in blacks compared to whites (19.4 vs 30.8 ng/ml, p<0.05). The prevalence of 25(OH)D deficiency (<15 ng/ml) was 16.2% overall, but 6.6% among whites and 32.3% among blacks [Table 3].

Fatal stroke rate was higher among 25(OH)D deficient individuals vs those with levels ≥15 ng/ml (1.81 vs 0.84 per 1000 person-years, respectively) [Table 3]. The HRs for fatal stroke associated with 25(OH)D deficiency (<15 ng/ml) are shown in Table 3, and were similar across all 3 multivariable models tested. For the fully-adjusted model 3, 25(OH)D

deficiency was associated with an increased risk of fatal stroke in whites [HR 2.13 (95% CI 1.01–4.50)] but not in blacks [0.93 (0.49–1.80)], p-interaction=0.20.

In age and sex adjusted models, the HR for fatal stroke associated with black compared with white race was 1.76 (1.19–2.60), and it was only modestly attenuated after further adjustment for socio-economic status and CVD risk factors [1.60 (1.01–2.53)] {results not shown in Tables}. Since low 25(OH)D levels were not related to stroke in blacks, they cannot explain the higher stroke incidence in blacks. Adjustment for 25(OH)D levels would be inappropriate in the absence of a similar association with stroke in both racial groups.

Discussion

In 2004, there were 5.7 million adult stroke survivors in the US (2.6%), with 700,000 new or recurrent strokes occurring annually.[14] The direct/indirect cost of stroke in 2007 was estimated to be $62.7 billion.[14] Thus, finding novel risk factors for the prevention and treatment of stroke, such as potentially 25(OH)D deficiency, is of upmost public health importance.

Only a few prior studies have evaluated the association of 25(OH)D levels with cerebrovascular events. In a small case-control study, 44 stroke patients had lower 25(OH)D levels than healthy elderly controls.[2] In the Ludwigshafen Risk and Cardiovascular Health prospective study of Germans referred for coronary angiography, low levels of both 25(OH)D and 1,25(OH)2D predicted incident fatal stroke.[3] Low 25(OH)D was found to be associated with cerebrovascular death in a Finish study[22] and linked to incident stroke among a general health care population in Utah.[23] Stroke events were included in a composite outcome linking 25(OH)D deficiency to incident CVD events in the Framingham Offspring study, although it was not a separate outcome.[1] However, the relationship of 25(OH)D with stroke among black race/ethnicity has not been previously reported to our knowledge.

In this large biracial population-based study, we found that 25(OH)D deficiency was independently associated with increased risk of fatal stroke among whites but not blacks. This association in whites remained even after potential cofounders and mediators were taken into account. However, the qualitative difference in the 25(OH)D association with stroke by race was not expected. Notably, we did not find higher 25(OH)D levels to be inversely associated with the traditional CVD risk factors of diabetes, hypertension, and hypercholesterolemia in blacks; whereas 25(OH)D was inversely associated with these factors among whites.

The reason for the lack of association of 25(OH)D and fatal stroke in blacks is uncertain, though there are several possible explanations. First, the study may have been underpowered to see an association in blacks with only 60 events. Secondly, among stroke cases, blacks historically have a higher proportion of hemorrhagic events than do whites.[16] It is conceivable that the relation of 25(OH)D to stroke risk is differential by stroke subtype. In our analysis we were unable to distinguish between hemorrhagic and ischemic strokes. Third, the distribution of 25(OH)D values was narrower among blacks than among whites, which would make it more difficult to detect an statistical association among blacks.

Lastly, there is evidence to suggest that blacks have adapted a relative resistance to the adverse effects of 25(OH)D deficiency. For example, despite their low 25(OH)D levels, it is thought that blacks have lower rates of fractures because of a skeletal resistance to the actions of PTH.[10] Prior work from NHANES has suggested that the relationship between 25(OH)D, bone mineral density, and PTH may differ by race.[24] These authors found that PTH was inversely associated with 25(OH)D only at low levels (<20 ng/ml) in blacks,

whereas in whites, PTH was inversely associated with 25(OH)D throughout the range of 25(OH)D. These data suggest that the optimal range of 25(OH)D for whites may not be the same as for blacks.[24] However, current guidelines do not recommend different levels according to race or skin color.[8]

Our study has confirmed prior studies by again showing that blacks had a higher rate of stroke than whites, and this racial disparity persists after traditional CVD risk factors and lifestyle factors were taken into account. We did not find that racial differences in 25(OH)D levels could explain the higher stroke incidence in blacks. In contrast to our findings, a prior publication also using data from NHANES-III found that racial differences in 25(OH)D levels partially attenuated the higher age-sex adjusted CVD mortality rates seen in blacks compared to whites.[25] That study included all CVD ICD-10 codes I11-78 and did not separate out stroke specifically and only included fatal events through December 2000.

Several possible biologic mechanisms might explain the association of vitamin D deficiency with stroke. Activated vitamin D is an inhibitor of the renin-angiotensin system.[26] Lower 25(OH)D levels are associated with increased risk of incident hypertension,[27] as well as diabetes. [28] Activated vitamin D may also retard atherosclerosis by inhibiting macrophage cholesterol uptake and foam cell formation.[29] Vitamin D receptors are ubiquitously located throughout the brain and arterial vasculature. Buell et al recently reviewed the many ways that vitamin D may confer neuroprotection including inhibition of inducible nitric oxide synthase (which is upregulated during ischemic events), antioxidation, and anti-inflammatory mechanisms.[30]

A limitation of our study is that NHANES-III study design did not ascertain incident non-fatal stroke. Only mortality outcomes were available through linkage with the National Death Index. Fatal stroke was identified by ICD-10 codes as listed on the death certificate, and there may be misclassification of how this outcome was recorded. Furthermore, this study was underpowered to evaluate sub-types of stroke (e.g. ischemic vs hemorrhagic). White matter disease and subclinical infarcts are also disproportionately found in excess in blacks compared to whites, but the association of subclinical cerebrovascular disease and 25(OH)D could not be assessed with the NHANES study design. 25(OH)D levels were also only measured once at baseline and may not be reflective of lifetime vitamin D status.

In summary, observational studies and biologic plausibility support a potential role for low vitamin D in the etiology of cerebrovascular disease. However it is currently unknown whether vitamin D supplementation at adequate doses can prevent stroke outcomes and whether there are racial differences in treatment effect. The large-scale VITAL study (Vitamin D and Omega-3 Trial) funded by the NIH, which began recruiting in 2010, will study this relationship.[31] Investigators plan to enroll 20,000 men (age>60) and women (age>65) in the US without CVD, one-quarter of whom will be black. The participants will be randomly assigned in a 2×2 factorial design to daily dietary supplements of vitamin D (2000 IU, a dose larger than those studied thus far), fish oil (1 gram of omega-3 fatty acids), their combination, or placebos. Primary outcomes include cancer and CVD incidence and mortality (including stroke) during a five-year follow-up period.

Conclusions

25(OH)D deficiency may increase the risk of stroke death in whites but not blacks. Clinical trials are warranted to determine whether treatment of 25(OH)D deficiency through supplementation and modest sunlight exposure can reduce stroke mortality.

Acknowledgments

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Table 1

Baseline characteristics by race and subsequent development of fatal stroke [Mean (SE mean) or % distribution]

	White			Black		
	All	Stoke	No Stoke	All	Stroke	No Stoke
Unweighted *N*	5001	116	4885	2980	60	2920
Weighted stroke prevalence per 100	1.24	x	x	1.47	x	x
Stroke rate of 1000 person-years	0.90	x	x	1.08	x	x
25(OH)D [ng/mL]	30.8(0.4)	27.4(1.3)	30.9(0.4)*	19.4(0.4)#	21.5(1.3)	19.4(0.4)
Age [years]	50.1(0.6)	73.4(1.4)	49.8(0.5)*	46.6(0.5)#	67.7(2.1)	46.3(0.5)*
Women	52.9	65.0	52.8*	56.4#	65.9	56.2
BMI [kg/m^2]	26.8(0.1)	26.6(0.5)	26.8(0.1)	28.2(0.2)#	27.9(0.8)	28.2(0.2)
Current smoker	26.9	13.7	27.0*	36.4#	31.6	36.4
Income< $25,000/year	32.3	62.1	31.9*	58.1#	82.4	57.7*
<High school education	19.5	28.3	19.4	33.7#	70.8	33.1*
Physical activity [times/month]	24.1(0.8)	20.3(3.5)	24.1(0.8)	20.8(0.8)#	15.3(3.4)	20.9(0.8)
Alcohol intake [times/month]	9.2(0.5)	9.0(3.5)	9.2(0.5)	9.4(0.5)	4.4(1.9)	9.4(0.5)*
Vitamin D supplement user	31.5	25.9	31.6	21.4#	21.2	21.4
Supplemental vitamin D intake among users [IU/d]	392.3(16.0)	406.7(60.0)	392.1(16.1)	407.2(24.4)	385.0(121.0)	407.6(24.7)
CRP [mg/dL]	0.4(0.01)	0.6(0.07)	0.4(0.01)*	0.5(0.02)#	0.6(0.1)	0.5(0.02)
GFR [ml/min per 1.73 m^2]	93.4(0.6)	78.2(2.5)	93.6(0.6)*	106.9(0.7)#	77.7(3.6)	107.4(0.7)*
Diabetes	5.9	12.4	5.8	8.9#	26.1	8.7*
Hypertension	27.6	65.3	27.2*	35.3#	87.0	34.5*
Hypercholesterolemia	25.1	46.42	24.8*	19.7#	43.2	19.4*

*
Significantly different from those in the same racial group with fatal stroke (p<0.05).

#
Significantly different from whites (p<0.05).

Table 2

Sample characteristics according to quartiles of 25(OH)D and race [Mean (SE mean) or % distribution]

	Serum 25(OH)D Quartile (ng/mL)				
	Whites (N=5001)				
	1(<22.0)	2(22.0–28.5)	3(28.6–35.9)	4(≥36)	P_{trend}
25(OH)D level, ng/mL	17.2(0.1)	25.4(0.1)	32.1(0.1)	44.7(0.3)	
Unweighted N	1208	1239	1265	1289	
Age [years]	53.7(0.8)	51.4(0.7)	49.4(0.7)	46.9(0.7)	<0.0001
Women	66.5	53.3	50.9	44.1	<0.0001
BMI [kg/m²]	28.2(0.3)	27.3(0.2)	26.5(0.21)	25.4(0.2)	<0.0001
Physical activity [times/month]	16.7(1.1)	21.7(1.0)	25.0(1.0)	30.8(1.3)	<0.0001
CRP [mg/dL]	0.48(0.02)	0.41(0.02)	0.37(0.02)	0.35(0.01)	<0.0001
GFR [ml/min per 1.73 m²]	91.8(1.0)	93.9(0.9)	93.7(0.9)	93.8(0.9)	0.14
Diabetes	8.9	6.9	4.4	4.1	<0.0001
Hypertension	35.0	29.3	26.2	22.0	<0.0001
Hypercholesterolemia	31.2	24.9	23.1	22.3	0.0002
	Blacks (N=2980)				
	1(<13.6)	2(13.6–17.9)	3(18.0–24.1)	4(≥24.2)	
25(OH)D level, ng/mL²	10.6(0.1)	15.8(0.04)	20.8(0.1)	31.4(0.4)	
Unweighted N	742	741	757	740	
Age [years]	44.8(0.6)	46.6(0.7)	46.8(0.7)	48.4(0.8)	0.0006
Women	69.3	59.2	48.7	47.4	<0.0001
BMI [kg/m²]	28.9(0.3)	28.7(0.4)	28.0(0.3)	27.3(0.3)	<0.0001
Physical activity [times/month]	16.1(0.9)	18.3(1.1)	23.4(1.4)	26.0(1.5)	<0.0001
CRP [mg/dL]	0.56(0.03)	0.55(0.03)	0.51(0.04)	0.47(0.02)	0.021
GFR [ml/min per 1.73 m²]	111.3(1.4)	106.6(1.3)	106.4(1.1)	103.1(1.2)	<0.0001
Diabetes	7.4	9.6	9.4	9.5	0.22
Hypertension	31.9	35.4	37.3	36.8	0.08
Hypercholesterolemia	15.2	20.4	21.1	22.4	0.008

Table 3

HRs (95% CI) for fatal stroke for those with 25(OH)D levels <15 ng/ml compared to ≥15 ng/mL

	All	Whites	Blacks	
N	7981	5001	2980	
Prevalence of 25(OH)D deficiency (%)	16.2	6.6	32.3	
Number of strokes for 25(OH)D<15 ng/ml	35	20	15	
Stroke rate per 1000 person-years				
25(OH)D<15 ng/ml	1.81	2.57	0.90	
25(OH)D≥15 ng/ml	0.84	0.81	1.17	
				p-race interaction
Model 1: HR(95% CI)	1.73(1.08–2.79)	2.04(1.23–3.40)	1.02(0.53–1.95)	0.05
Model 2: HR(95% CI)	1.68(0.90–3.13)	2.09(1.98–4.43)	0.88(0.45–1.73)	0.10
Model 3: HR(95% CI)	1.74(0.94–3.20)	2.13(1.01–4.50)	0.93(0.49–1.80)	0.20

Model 1 adjusts for age and sex; Model 2 adjusts for covariates in Model 1 plus income, education, BMI, smoking, physical activity, alcohol use, and season; Models 3 adjusts for covariates in Model 2 plus CRP, diabetes, hypertension, and hypercholesterolemia. For results for the total population, models 1–3 are also adjusted for race.