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Vitamin D and aneurysmal subarachnoid hemorrhage: a UK Biobank Study

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Research Article

Keywords: subarachnoid hemorrhage, incidence, vitamin D, UK Biobank

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11165069/v1

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Abstract

Background

Vitamin D deficiency has been increasingly reported to be associated with aneurysmal subarachnoid hemorrhage (SAH). Mostly, vitamin D was measured after SAH has occurred after prolonged neurocritical care. We investigated the association between vitamin D levels and subsequent SAH in the UK Biobank cohort.

Methods

We retrieved data from the UK Biobank, a population-based cohort study of 502,411 participants, initiated in 2006. Serum vitamin D levels were classified as normal (≥ 50nmol/L), low (< 50nmol/L), and very low (< 30nmol/L). The primary outcome was SAH during study follow-up. We calculated SAH incidence ratios and performed logistic regression, adjusted for vascular risk factors.

Results

During the 16-year study follow-up, 766 SAH were recorded. SAH incidence was 12.37 / 100,000 patient-years. Compared with normal vitamin D levels, adjusted odds ratios (OR) for SAH were 1.15 (95% CI 0.95–1.40) for very low, and 1.04 (95% CI 0.90–1.21) for low vitamin D levels.

Conclusion

In this large-scale analysis of the UK Biobank, we did not observe a significant association between vitamin D and SAH. Contrary to previous mostly small single-center reports, our findings suggest that vitamin D deficiency is unlikely to be a major independent risk factor associated with SAH.

Introduction

Intracranial aneurysms (IA) develop during life and, in the event of rupture, result in aneurysmal subarachnoid hemorrhage (SAH).[1] SAH accounts for only 5-10% of all strokes, however, SAH has a high rate of morbidity and mortality globally.[2] The mechanisms leading to the development and rupture of intracranial aneurysms are not yet completely understood. Inflammatory processes have been identified as contributors leading to SAH. [3]

There is growing evidence that vitamin D has anti-inflammatory effects.[4] In a previous study, we observed that SAH incidences were higher in regions with lower ultraviolet (UV) radiation exposure levels.[5] Since UV radiation induces vitamin D synthesis, this finding suggests a potential link between low vitamin D levels and SAH incidence. So far, mostly small, single-center studies have reported an

association between vitamin D and SAH. [6,7] They measured vitamin D after hemorrhage has occurred. This led to the question whether low vitamin D could serve as a potential risk factor for SAH versus it being a possible consequence of SAH and subsequent critical illness. To address this, we investigated the association between vitamin D — measured at baseline, before any SAH event — and subsequent SAH incidence in the UK Biobank.

The UK Biobank is a large prospective population-based cohort study of 502,411 participants across the United Kingdom.[8] Since 2006, prospective clinical data have been collected including blood samples.[9] In the current analysis, we included all participants from the UK Biobank with available vitamin D levels. Among those participants, we identified those with SAH and excluded participants with SAH occurrence before the study period as well as without SAH bleeding date. SAH cases were defined as participants with International Statistical Classification of Diseases and Health-Related Problems (ICD) codes I60.0 to I60.9 during study follow-up. All participants provided written informed consent, and the study was approved by the North West Multicenter Research Ethics Committee and the National Health Service National Research Ethics Service (ref 11/NEW/0382).

Serum concentrations of vitamin D called 25-hydroxyvitamin D (25(OH)D), were measured using a direct competitive chemiluminescent immunoassay method at UK Biobank's purpose-built facility. 25(OH)D is the circulating form of vitamin D in the blood, thus the indicator of vitamin D status in the body and is hereafter referred to as vitamin D level.[10] The UK Biobank collected vitamin D at baseline. [9] Information on lifestyle factors, medical and family history, and medication use was retrieved from a self-completed questionnaire at the baseline assessment visit for UK Biobank. The UK Biobank methodology has been described previously.[11] An exploratory analysis of quantitative baseline characteristics with mean (standard deviation) was performed. Qualitative data are described by their absolute and relative frequencies. We classified the participants into three categories depending on vitamin D levels: normal ($\geq$ 50nmol/L), low (<50 nmol/L) and very low (<30 nmol/L) vitamin D levels.[12] We determined SAH incidences for the overall study cohort as well as for the different groups of vitamin D levels and calculated incidence rate ratios (IRR) with corresponding 95% confidence intervals (95% CI). The incidence of SAH was calculated from the time participants were recruited until the end of the study period in 2022 including exclusion due to death from other causes than SAH during study period. Univariable logistic regression analysis with calculation of odds ratios (ORs) with corresponding 95% CI was performed to compare the occurrence of SAH for different levels of vitamin D during study follow-up. We compared how risk factors of SAH such as age, sex, ever-smoking status, alcohol consumption, systolic blood pressure and family history of stroke, including SAH differed between the cohorts.[13] We added multivariable regression models adjusted for the common risk factors tested as significant in the previous univariable regression analysis and vitamin D levels. A priori level of significance was set at $p < 0.05$ (two-sided). All analyses were carried out with SAS (SAS Institute, Version 9.4).

We included 477,815 participants from the UK Biobank cohort. From the original cohort of 502,411 participants, 53,195 participants without SAH did not have a measurement of vitamin D levels. Among

those diagnosed with SAH, participants were excluded for the following reasons: They did not have vitamin D level measurements, had an SAH occurrence prior to study enrollment, or did not have a documented SAH date.

Since study recruitment in 2006, 766 (0.17%) participants developed SAH during follow-up until 2022. Supplementary Table 1 summarizes the baseline characteristics of the study population of the UK Biobank, including common SAH risk factors and potential confounders for both SAH and vitamin D status. 426 SAH cases were observed with low vitamin D levels vs. 340 with normal vitamin D levels. 176 SAH cases had very low vitamin D levels. SAH incidences were reported as 12.37 per 100,000 patient-years overall. Within the three categories of vitamin D levels, SAH incidence was highest among the study cohort with very low vitamin D levels, 13.74 per 100,000 patient years. Low vitamin D levels reported a SAH incidence of 12.51 per 100,000 patient years, and normal vitamin D levels reported a SAH incidence of 12.21 per 100,000 patient years (Table 1). For participants with low vitamin D levels, SAH incidence was 2% higher than in those with normal vitamin D levels (IRR = 1.02, 95% CI = 0.89 - 1.18). For participants with very low vitamin D levels, SAH incidence was 13% higher than in those with normal vitamin D levels (IRR = 1.13, 95% CI = 0.94 - 1.35).

In the univariable logistic regression analysis, common vascular risk factors were tested (Table 2a). All common risk factors proved to be significant except for alcohol consumption. We included all significant risk factors as parameters for the multivariable regression analysis. Vitamin D did not show a significant association with SAH occurrence regardless of vitamin D levels. Multivariable regression analysis for modelled probability of SAH occurrence and adjustment to common risk factors was significant for age, sex, and smoking across the study cohort (Table 2b). A non-significant increase of OR was observed with decreasing vitamin D levels: normal vs. low vitamin D levels OR 1.04 (95% CI 0.90 - 1.21), normal vs. very low vitamin D levels OR 1.15 (95% CI 0.95 - 1.40), and normal and low vs. very low vitamin D levels OR 1.18 (95% CI 0.98 - 1.41).

In this large-scale analysis of the UK Biobank cohort, we found no significant association between SAH incidence risk and serum vitamin D levels. Very low vitamin D showed a slightly increased SAH risk: this association was not significant. Our findings suggest that vitamin D deficiency is unlikely to be a major independent risk factor associated with SAH. Our results are consistent with a recent Mendelian randomization study in a Chinese cohort which did not find a causal link between vitamin D levels and SAH. [15]

A primary strength of our study was the large size of our study cohort, especially when putting our analysis into context with existing evidence on SAH and vitamin D, mainly undertaken in single centers with retrospective data. Another strength is that we had a large number of participants with available vitamin D measurements. Also, we were able to adjust for several risk and confounding factors. There are several limitations to this study. It is known that SAH varies widely depending on the geographic region.[16,17] Our analysis was based to a population living in the United Kingdom, mainly with a Caucasian ethnicity, which may limit the generalizability of the findings to populations with different genetic and

environmental risk profiles.[18] In the UK Biobank, data were only available for vitamin D levels upon study inclusion, increasing regression dilution bias.

In this large-scale analysis of the UK Biobank, we did not observe a significant association between vitamin D and SAH. Contrary to previous mostly small single-center reports, our findings suggest that vitamin D deficiency is unlikely to be a major independent risk factor associated with SAH.

Abbreviations

25(OH)D
25-hydroxyvitamin D
95% CI
95% confidence intervals
IA
intracranial aneurysm
ICD
International Statistical Classification of Diseases and Health-Related Problems
IRR
incidence rate ratio
OR
odds ratio
SAH
aneurysmal subarachnoid hemorrhage
UV
ultraviolet

Declarations

Instructions to authors

The authors confirm that the manuscript complies with all instructions to authors and confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

Author contributions

Andia Mirbagheri: Conceptualization, Data Curation, Methodology, Investigation, Formal Analysis, Project administration, Validation, Visualization, Writing – original draft and review and editing **Svetlana Hetjens:** Data curation, Formal Analysis, Methodology, Software, Writing – review and editing **Jos P Kanning**: Conceptualization, Data Curation, Methodology, Writing – review and editing. **Kristiina Rannikmae**.**:** Conceptualization, Resources, Writing – review and editing**: Ynte Ruigrok**: Conceptualization, Methodology, Resources, Validation Writing – review and editing.: **Gabriel Rinkel:** Conceptualization, Methodology, Formal Analysis, Project administration, Supervision, Validation, Writing- reviewing and

editing. Authorship requirements were met. All authors read and approved the final manuscript as well as agreed to publish a preprint. This manuscript has not been published elsewhere and is not under consideration by another journal.

Ethical Approval

All participants provided written informed consent, and the study was approved by the North West Multicenter Research Ethics Committee and the National Health Service National Research Ethics Service (ref 11/NEW/0382).

Artificial Intelligence statement

The authors confirm that no generative artificial intelligence tools or large language models were used in the research or writing of this work.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability

Relevant data is available within the article. On reasonable request, further data is available.

Reporting Checklist

The authors confirm the use of the STROBE as a reporting checklist.

Funding for the study

No funding was acquired for this study.

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Tables

Table 1 SAH incidences and incidence rate ratios

The table provides SAH incidences and incidence rate ratios (IRR) with 95% confidence intervals (95% CI) of overall cohort and participants with normal, low and very low vitamin D levels

	All	Vitamin D ≥50 nmol/l	Vitamin D <50 nmol/l	Vitamin D <30 nmol/l
No. of SAH	766	340	426	176
SAH incidence per 100,000 patient years	12.37	12.21	12.51	13.74
IRR (95% CI)		**Vitamin D >50 vs. <50 nmol/**		**Vitamin D >50 vs. <30 nmol/**
		1.02 (0.89 - 1.18)		1.13 (0.94 - 1.35)

Table 2 Logistic regression analysis for vascular risk factors for SAH and normal, low and very low vitamin D levels

Table 2a.

Univariable logistic regression for modelled probability of occurrence of SAH.

Characteristic	All OR (95% CI)
Age at recruitment (years)	1.03 (1.02 - 1.04)*
Normal vs. low vitamin D level (nmol/l)	1.01 (0.88 - 1.17)
Normal vs. very low vitamin D level (nmol/l)	1.10 (0.92 - 1.32)
Low and normal vs. very low vitamin D (nmol/l)	1.12 (0.95 - 1.32)
Sex (F in %)	1.40 (1.21 - 1.62)*
Systolic blood pressure (mmHg)	1.01 (1.00 - 1.01)*
Smoking (ever smoked, yes in %)	1.23 (1.06-1.43)*
Alcohol consumed (low-moderate vs high consummation)	0.91 (0.79 - 1.05)
Family history of stroke (yes in %)**	0.81 (0.70 - 0.95)*

*p<0.05 = statistically significant

** including ischemic and hemorrhagic stroke

Table 2b.

Multivariable logistic regression for modelled probability of occurrence of SAH adjusted for previously tested significant common risk factors age, sex, blood pressure, smoking, family history of stroke. Moreover, vitamin D has been also included.

Characteristic	OR (95% CI) Vitamin D ≥50 vs <50 nmol/l	OR (95% CI) Vitamin D ≥50 vs. <30 nmol/l	OR (95% CI) Vitamin D <30 vs. >30 nmol/l
Age at recruitment (years)	1.03 (1.02 - 1.04)*	1.03 (1.02 - 1.04)	1.03 (1.02 - 1.04)*
Vitamin D level (nmol/l)	1.04 (0.90 - 1.21)	1.15 (0.95 - 1.40)	1.18 (0.98 - 1.41)
Sex (F in %)	1.53 (1.31 - 1.79)*	1.49 (1.23 - 1.79)*	1.53 (1.31 - 1.79)*
Systolic blood pressure (mmHg)	1.00 (1.00 - 1.01)	1.00 (1.00 - 1.01)	1.00 (1.00 - 1.01)
Ever smoking (yes%)	1.25 (1.08 – 1.47)*	1.25 (1.04 - 1.54)	1.25 (1.06 – 1.47)*
Family history of stroke (%)	0.89 (0.76 - 1.05)	0.87 (0.71 - 1.06)	0.89 (0.76 - 1.05)

*p<0.05 = statistically significant

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklist.docx
- SupplementaryTable1.docx