**Acetylsalicylic acid and subarachnoid haemorrhage in the Nurses’ Health Study**

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**Abstract**

**Background**

Acetylsalicylic acid is known to increase the risk of bleeding throughout the body. However, there is also evidence to suggest that acetylsalicylic acid may have a protective role in the formation and rupture of intracranial aneurysms. Previous studies investigating acetylsalicylic acid and subarachnoid haemorrhage (SAH) have so far provided conflicting results.

**Aims**

The aim of this study was to analyse the Nurse’s Health Study (NHS) using serial assessments to evaluate differences in rates of SAH in those participants taking acetylsalicylic acid and those not taking acetylsalicylic acid while considering dose, frequency, and duration as well as different types of SAH.

**Methods**

The Nurse’s Health Study (NHS) is a prospective population-based cohort study of female nurses. Information on acetylsalicylic acid was first reported in 1980 until 2016 and included acetylsalicylic acid use, dose, frequency and duration. All stroke cases were classified by physicians. Cox proportional-hazards regression models were used to estimate the hazard ratio (HR) associated with acetylsalicylic acid use.

**Results**

A total of 117,648 NHS participants were eligible for analysis with 357 cases of SAH observed over 4,091,239 years of follow up. There was no association between acetylsalicylic acid use and SAH (HR 1.02 [0.82, 1.28], p=0.85), aneurysmal SAH (1.04 [0.78, 1.39], p=0.78), or idiopathic SAH (HR 0.94 [0.65, 1.34], p=0.72). The number of acetylsalicylic acid tablets per week was associated with SAH (HR 1.03 [1.00, 1.06], p=0.02), specifically fatal SAH (HR 1.04 [1.00, 1.08], p=0.03). There was no association between frequency and SAH (HR 1.06 [0.99, 1.13], p=0.07).

**Conclusions**

There was no evidence to support a protective association between acetylsalicylic acid and either SAH or aneurysmal SAH in female participants. In fact, there was some evidence to suggest increased SAH risk with increased acetylsalicylic acid dose in some but not all analyses.

**Data access statement**

Data are available by request from the Brigham and Women's Hospital, Harvard Medical School, and Harvard T.H. Chan School of Public Health.

**Introduction**

Spontaneous subarachnoid haemorrhage (SAH) is a rare form of stroke associated with significant morbidity and mortality(1). The rupture of intracranial aneurysms accounts for the majority of cases. Identified incidentally, unruptured aneurysms can be treated prophylactically with neurosurgical or endovascular procedures. However, the risks of these treatments are often not justified hence many cases are managed conservatively. For these patients there are no medical options to reduce the risk of rupture.

Due to its antiplatelet effects, acetylsalicylic acid is known to increase the risk of bleeding throughout the body(2). Clinicians have historically avoided its use in patients with aneurysms. However, there is growing evidence to suggest that inflammation is involved in the formation and rupture of intracranial aneurysms and that acetylsalicylic acid can attenuate key pathways involved in this process(3). Observational studies and meta-analyses investigating this association have provided conflicting results(4-8). A recent meta-analysis found considerable variation in studies of patients with known aneurysms and no association in the general population partially explaining this heterogeneity(9).

The biggest challenge for all these studies is ascertaining acetylsalicylic acid use in an unbiased way prior to aneurysm rupture. As highlighted in our analysis of the UK Biobank, while baseline information on acetylsalicylic acid use is often assumed to be constant realistically there are changes during follow up(10). One of the only studies to date with serial assessments of acetylsalicylic acid use was an analysis of the Framingham Heart Study in which participants were followed up for up to 298,790 person-years(11). Ultimately, this study was underpowered demonstrating how difficult it is to obtain a large enough cohort to address this issue in the general population.

The Nurses’ Health Study (NHS) is the ideal cohort study to resolve the limitations of the existing literature as it provides a large sample size and serial follow up. An analysis of the relationship between acetylsalicylic acid use and stroke was performed in 1999 using a pooled logistic regression model on data up until 1994(12). This analysis was underpowered, with the significant findings only seen in some subgroups (increased SAH risk in participants taking over 15 acetylsalicylic acid tablets per week). Since this analysis there has been over 20 years of further follow up and over five times as many SAH events now available.

Another criticism of the existing literature is that most cohort studies have limited information regarding acetylsalicylic acid dose, frequency, and duration, all of which are recorded in the NHS. In addition, previous studies do not differentiate between aneurysmal and non-aneurysmal SAH which is carefully categorised in the NHS. While there is a pathophysiological basis for a protective effect in aneurysmal cases, this is not true for other forms of spontaneous SAH. Recently published work has attempted to address this issue with some success, but further research is required(10, 11).

Subsequently, the aim of this study was to analyse the NHS using serial assessments to evaluate differences in rates of SAH in those participants taking acetylsalicylic acid and those not taking acetylsalicylic acid while considering acetylsalicylic acid dose, frequency, and duration as well as different types of SAH.

**Methods**

The NHS is a prospective population-based cohort study of female nurses. Recruitment of participants started in 1976. Informed written consent was obtained. Eligibility criteria comprised of female nurses born between 1st January 1921 and 31st December 1946 (age 30-55) residing in 11 US states. Participants were followed up with mailed questionnaires every two years. The last available examination for this analysis was from 2016. **T**he NHS is funded by the National Institutes of Health (NIH). This study was approved by the institutional review board at the Brigham and Women’s Hospital. Anonymized data are available by request from the NHS.

***Acetylsalicylic acid***

Information on acetylsalicylic acid was first reported in 1980 until 2016. In this questionnaire, participants reported on acetylsalicylic acid use (current use yes/no), dose (number of tablets per week), and duration (years from first reported use to last reported use). From 1984 participants reported on frequency (number of days per week).

Subgroup analyses were performed stratifying acetylsalicylic acid dose (Past use, 1-2 tabs/ week, 3-5 tabs/ week, 6-14 tabs/ week, 15+ tabs/week, Current, unknown dose), frequency (Past use, 1 day/ week, 2-3 days/ week, 4-5 days/ week, 6+ days/ week, Current, unknown frequency), and duration (Current <5yr, Current 5-14yr, Current 15yr+, Past <5yr, Past 5-14yr, Past 15yr+).

Tablet dose in milligrams was initially not recorded in the cohort. However, as of the 1992 questionnaire, one tablet of acetylsalicylic acid was defined as equivalent to 300mg. In this analysis it was assumed that prior to 1992 one tablet was also 300mg. For this reason, we performed sensitivity analyses comparing low dose (75mg daily), intermediate dose (75mg to 300mg daily) or high dose (300mg or more daily) in patients pre and post 1992.

***Subarachnoid Haemorrhage***

All strokes were classified by physicians according to the National Survey of Stroke criteria. Stroke was defined as a neurological deficit with sudden or rapid onset that persisted for more than 24 hours or until death. Cases associated with pathology such as infection, trauma, or malignancy as well as asymptomatic cases identified on radiologic imaging were excluded. SAH was defined as haemorrhage in the subarachnoid space. SAH were further categorised using criteria from the Perth Community Stroke Study: aneurysm, arteriovenous malformation, or other. Participants who reported on incident stroke were asked to provide additional details by letter or interview. Subsequently, permission was asked to obtain medical records to confirm the diagnosis of stroke. Fatal events were recognized by reports from family, US Postal Service, or the National Death Index. Confirmation of fatal stroke cases relied on death certificates, medical records during hospitalization, or autopsy records.

***Analysis***

Cox proportional-hazards regression models were used to estimate the hazard ratio (HR) associated with acetylsalicylic acid use. Censoring events include SAH, death or last known follow up. The proportional hazards assumption was checked using graphical diagnostics based on the scaled Schoenfeld residuals. Multivariable analyses were conducted. All variables were included as time varying covariates. Multiple imputation was used to account for missing variables in the multivariable analysis. A stepwise variable selection procedure including forward and backward iterations was used to obtain the best final regression model for the multivariable analysis. The significance levels for entry (SLE) and for stay (SLS) equalled 0.15. Variables in the final model included age, smoking status, hypertension and body mass index (BMI). Non-linear regression analyses were performed using cubic splines. Statistical analysis was conducted in statistical software package R (R Core Team, 2020. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; [https://www.R-project.org/](https://www.r-project.org/)).

**Results**

A total of 117,648 participants from the NHS were eligible. There were 357 SAH cases over 4,091,239 years of follow up. The incidence of SAH was 8.73 per 100,000 (CI 7.84- 9.68) person years in this study. The incidence of aneurysmal SAH was 4.89 per 100,000 person years (CI 4.23- 5.62). The incidence of idiopathic SAH was 3.50 per 100,000 person years (CI 2.95- 4.12). The incidence of fatal SAH was 4.45 per 100,000 person years (CI 3.83- 5.14). The baseline characteristics of participants are shown in Supplementary Table 1.

***Acetylsalicylic acid use***

There was no significant association between acetylsalicylic acid use and SAH (HR 1.02 [0.82, 1.28], p=0.85) including the SAH subgroups. A Kaplan-Meier curve comparing the rates of SAH in the acetylsalicylic acid use groups is shown in Figure 1. The relationship between different measures of acetylsalicylic acid use, dose, frequency, and duration and SAH (including different subgroups) is shown in Table 1.

***Dose***

The number of acetylsalicylic acid tablets per week was associated with SAH (HR 1.03 [1.00, 1.06], p=0.02). Fatal SAH was similarly associated with dose (HR 1.04 [1.00, 1.08], p=0.03). Both aneurysmal SAH (1.03 [1.00, 1.07], p=0.08), and idiopathic SAH (HR 1.04 [1.00,1.08], p=0.07) were not significantly associated but showed trends in the same direction. Figure 2 shows a Kaplan Meier plot comparing the rates of SAH for different categories of acetylsalicylic acid dose. The association between individual dose categories and SAH is shown in Table 2 and Supplementary Table 2. No subgroups were associated with SAH. However, it is notable that the hazard ratio increases for each step up in acetylsalicylic acid dose and that the effect in lowest dose group (1-2 tablets a week) and the highest dose group (15+ tablets per week) is in the opposite direction. The results of the non-linear analysis using cubic splines are shown in Supplementary Figure 1.

***Frequency***

Participants reported on frequency from 1984 and, subsequently, 114,743 participants were included in this analysis. The number of days per week taking acetylsalicylic acid was not associated with SAH (HR 1.06 [0.99, 1.13], p=0.07). No relationship was found between acetylsalicylic acid frequency and aneurysmal SAH (HR 1.03 [0.94, 1.13], p=0.49), however, there was a significant finding for idiopathic SAH (HR 1.11 [1.00, 1.23], p<0.05). Frequency was not associated with fatal (HR 1.09 [0.99, 1.20], p=0.07) or non-fatal cases (HR 1.03 [0.95, 1.13], p=0.46). Similar to acetylsalicylic acid dose, subgroup analysis did not reveal any specific acetylsalicylic acid frequency associated with SAH, although hazard ratios generally increased with each step up in frequency (Figure 3, Supplementary Table 3).

***Duration***

Duration of acetylsalicylic acid use was not associated with SAH (HR 1.00 [0.99, 1.01]), nor was there any association with any SAH subgroup (Supplementary Figure 2, Supplementary Table 4).

***Sensitivity analyses***

We performed sensitivity analyses to reproduce the findings of Iso et al and see if different methodology would alter our findings. At that time, they reported a significant association between acetylsalicylic acid dose and SAH.(12). They did not describe any analysis of acetylsalicylic acid use, frequency or duration. This study used multivariate pooled logistic regression models to analyse time to event data rather than Cox proportional hazard models as used in our analysis. Although specific methodological detail is limited, we replicated their analysis as closely as possible and limited our follow up until 1994 including information on variables reported in the 1980, 1982, 1984, and 1988 questionnaires.

Using similar methodology to Iso et al, there was a trend in the direction of their results, but we were unable to demonstrate significance (p=0.05) (Supplementary Table 5). Acetylsalicylic acid use (on which they did not report) showed no association (p=0.74) similar to our findings. Replicating their methods but using the full dataset up until 2016 showed similar results to our primary analysis with no significant association between acetylsalicylic acid use and SAH but an association for acetylsalicylic acid dose, albeit not in the stratified analysis (Supplementary Table 6).

Further exploratory analyses were performed investigating acetylsalicylic acid dose. We performed analyses comparing low dose (75mg daily), intermediate dose (75mg to 300mg daily) and high dose (300mg or more daily). This analysis found a significant protective association between low dose acetylsalicylic acid and SAH (HR 0.69 [0.48- 0.99], p<0.05) (Supplementary Table 7). However, this was not replicated when analyses were limited to those cases occurring after the 1992 questionnaire after which it was specified that 1 tablet of acetylsalicylic acid was considered equivalent to 300mg (Supplementary Table 8).

**Discussion**

Despite not showing a relationship between acetylsalicylic acid use and SAH, we observed a significant association between dose and SAH. While these results create a paradox that is difficult to explain, it appears to rule out a protective effect of acetylsalicylic acid in the general population.

Two previous studies have conducted survival analyses investigating the association between acetylsalicylic acid and SAH in participants with known aneurysms and reported a protective association(13, 14). Subsequent longitudinal studies in healthy volunteers have provided conflicting results with weak evidence to support both an increased and decreased risk of SAH(10, 11). Analysis of the UK Biobank found an association between acetylsalicylic acid and fatal SAH(10). Despite this, these studies are limited by either sample size, definitions of SAH, or lack of serial follow up. This analysis of the NHS is the first study to examine the effects of acetylsalicylic acid dose, frequency, and duration on all forms of SAH.

We suggest that there are four possible hypotheses which explain our findings. Firstly, it is possible that the analysis is underpowered. While this is unlikely given the size of the cohort, even if this was the case the effect size would be too small to be clinically relevant. Our second hypothesis is that the association for acetylsalicylic acid dose is a false positive finding. While this is possible, there was a notable trend in the results meaning we are reluctant to definitively conclude that there is no relationship between acetylsalicylic acid and SAH at all. Our third hypothesis relates to the lower rate of SAH in participants taking low dose acetylsalicylic acid and the high rate of SAH in those taking high dose acetylsalicylic acid. While we were not sufficiently powered to show significant results in this subgroup analysis, these results may explain why we were unable to find an influence of acetylsalicylic acid use alone. However, the mechanism by which acetylsalicylic acid could reduce SAH risk at low doses but increase risk at high doses is difficult to explain. If anything, previous studies have suggested that any effect of acetylsalicylic acid on aneurysm rupture increases with acetylsalicylic acid frequency and dose(14, 15). Subsequently, our fourth hypothesis is that low dose acetylsalicylic acid does not in itself reduce SAH, but that people taking regular low dose acetylsalicylic acid may be more health conscious (and in particular more likely to have stopped smoking) and by virtue at lower risk of SAH.

Unfortunately, there is no simple way to resolve which of these hypotheses is correct. There are no larger studies available in the general population with the required data on acetylsalicylic acid and SAH, and further meta-analyses including existing studies would reinforce the message that acetylsalicylic acid use is not associated with SAH given the results of recent studies(10). Moreover, there are inevitable limitations of these observational studies and while we have conducted multivariate analyses, it is possible that confounding factors, such as smoking or other medications, are influencing the results(16). Similarly, previous researchers have strongly supported the view that there is a protective relationship having conducted animal studies, observational studies in patients with UIA and provided valid criticisms of these conflicting studies(14, 17-21). However, practically we conclude that although we cannot exclude a small effect of acetylsalicylic acid, there is no effect large enough to be clinically relevant in the general population.

***Aneurysmal and idiopathic SAH***

It has been hypothesised that different relationships between acetylsalicylic acid and different types of SAH exist(9). While there is evidence to suggest a protective mechanism for aneurysmal cases, there is no evidence available for non-aneurysmal SAH cases. Given its antiplatelet effects it is more likely that acetylsalicylic acid will increase the risk of non-aneurysmal SAH. It is also possible these differences, if present, may be more apparent with changes in acetylsalicylic acid dose, frequency and duration. We found some evidence to support a negative relationship between acetylsalicylic acid dose and both aneurysmal and non-aneurysmal SAH. Similar findings were present for acetylsalicylic acid frequency, with a significant association between frequency and idiopathic SAH. Overall, we found no evidence for a different relationship when comparing aneurysmal and non-aneurysmal cases.

***Fatal SAH***

The significant association between acetylsalicylic acid dose and fatal SAH is an important finding of this study. Previous studies investigating the association between acetylsalicylic acid and SAH in patients with intracranial aneurysm have found a protective relationship(9). However, this literature is dominated by case-control studies at risk of selection bias as they fail to account for poor grade cases resulting in death outside of hospital or not requiring transfer to tertiary neurosurgical units. Our finding in the NHS may partially explain the findings of these studies, as acetylsalicylic acid may increase the severity of SAH. Further studies are required to examine the association between acetylsalicylic acid and objective measures of SAH severity such as the WFNS grade and Fisher scale.

***Strengths and Limitations***

When compared with previous studies, there are many strengths to the NHS. In terms of study design, as opposed to the large number of case- control studies which have preceded this paper, the NHS is a large prospective longitudinal cohort with serial follow up. A comprehensive acquisition of a SAH including cases from death registry records ensures minimal selection bias and the classification of SAH cases allows for analyses comparing aneurysmal and non-aneurysmal cases.

Despite this, several limitations remain. As with any observational study, our analysis carries a risk of bias due to differences between groups. While there remains no data available from randomized controlled trials, there are three currently ongoing. With the target recruitment of 58 participants complete, the Unruptured Intracranial Aneurysm Aspirin Trial (UIAAT, NCT 03661463) is a phase 2 study examining the effects of 300mg of acetylsalicylic acid on inflammation within the aneurysm wall using MRI vessel wall imaging. With recruitment ongoing, the Prospective Randomized Open-label Trial to evaluate risk faCTor management in patients with Unruptured intracranial aneurysms trial (PROTECT-U, NCT 0306354) is a phase 3 study planning to recruit 776 participants with the aim to investigate the effects of 100mg of acetylsalicylic acid and intensive blood pressure management (<120mmHg) on growth or rupture after three years(22). Lastly, the Aspirin Treatment for Small Unruptured InTracranial Aneurysms With Ischemic cereBrovascuLar diseasE trial (AT-SUITABLE, NCT 05907902) which has started recruitment is a phase 3 study with a target of 824 participants aiming to examine the effects of 100mg of acetylsalicylic acid on growth and rupture at 2 years. While completion of these studies will provide further clarity, other large longitudinal studies, such as the Risk of Aneurysm Rupture study (ROAR) which has recruited over 20,000 participants with baseline data on acetylsalicylic acid use and linkage to primary care records to allow tracking of acetylsalicylic acid prescriptions over time, will also add to the evidence for or against acetylsalicylic acid(23).

It is also important to note that the NHS only includes female patients. While the effect of acetylsalicylic acid on aneurysm rupture is greater in both male humans and mice, previous animal studies have also shown beneficial effects on vasculature, including antioxidative effects, stabilization of endothelial cells, and anti-inflammatory effects in post-menopausal females(17, 24). In this cohort, no significant differences in the effect of acetylsalicylic acid use between the two groups (premenopausal: (HR 0.82 [0.44- 1.53], p=0.51), postmenopausal: (HR 1.14 [0.88- 1.46], p=0.32)), although it is important to note that only 14% of examinations were conducted in premenopausal participants. The presence of intracranial aneurysms was also not reported on in the NHS. It is therefore not possible to generalise these results to patients with known aneurysms and the risk associated with giving patients with unruptured aneurysms acetylsalicylic acid cannot be ascertained from this study.

Lastly, the definition of idiopathic in the NHS obtained from the Perth Community Stroke Study includes cases that could not definitively be attributed to an aneurysm or arteriovenous malformation. It is possible it included aneurysmal SAH cases as is likely to have included some cases of fatal SAH in whom angiography was not undertaken.

***Conclusion***

In this analysis of the NHS, we found no evidence to support a protective association between acetylsalicylic acid and either SAH or aneurysmal SAH. While we can be confident of this in the general population and in females, it does not necessarily apply to people with known UIA or males. There was some evidence to suggest increased SAH risk with increased acetylsalicylic acid dose in some but not all analyses.

**Acknowledgments**

None.

**Author contributions**

FE was involved in the conceptualisation, methodology, formal analysis, and writing the manuscript.

SH and BG were involved in reviewing and editing the manuscript.

DB was involved in the conceptualisation, reviewing and editing the manuscript, and supervision.

**Statements and declarations**

**Ethical considerations:** Institutional review board at The Channing Division of Network Medicine, Brigham and Women’s Hospital approved this study.

**Consent to participate:** Informed consent was obtained from participants.

**Consent for publication:** Not applicable.

**Declaration of conflicting interest:** Not applicable.

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**Data availability:** Data are available upon request.

**References**

1. de Rooij NK, Linn FH, van der Plas JA, et al. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.

2. Cloud GC, Williamson JD, Thao LTP, et al. Low-Dose Aspirin and the Risk of Stroke and Intracerebral Bleeding in Healthy Older People: Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2023;6(7):e2325803.

3. Chalouhi N, Ali MS, Jabbour PM, et al. Biology of intracranial aneurysms: role of inflammation. J Cereb Blood Flow Metab. 2012;32(9):1659-76.

4. Phan K, Moore JM, Griessenauer CJ, et al. Aspirin and Risk of Subarachnoid Hemorrhage: Systematic Review and Meta-Analysis. Stroke. 2017;48(5):1210-7.

5. Qian C, He Y, Li Y, et al. Association Between Aspirin Use and Risk of Aneurysmal Subarachnoid Hemorrhage: A Meta-analysis. World Neurosurg. 2020;138:299-308.

6. Shimizu K, Aoki T, Etminan N, et al. Associations Between Drug Treatments and the Risk of Aneurysmal Subarachnoid Hemorrhage: a Systematic Review and Meta-analysis. Transl Stroke Res. 2022.

7. Florez WA, García-Ballestas E, Maeda F, et al. Relationship between aspirin use and subarachnoid hemorrhage: A systematic Review and meta-analysis. Clin Neurol Neurosurg. 2021;200:106320.

8. Yang S, Liu T, Wu Y, et al. The Role of Aspirin in the Management of Intracranial Aneurysms: A Systematic Review and Meta-Analyses. Front Neurol. 2021;12:646613.

9. Ewbank F, Birks J, Bulters D. A meta-analysis of aspirin and subarachnoid hemorrhage in patients with intracranial aneurysms yields different results to the general population. Int J Stroke. 2022;17(3):341-53.

10. Ewbank F, Birks J, Gaastra B, et al. Aspirin and Subarachnoid Haemorrhage in the UK Biobank. Transl Stroke Res. 2023;14(4):490-8.

11. Ewbank F, Birks J, Bulters D. The association between acetylsalicylic acid and subarachnoid haemorrhage: the Framingham Heart Study. Sci Rep. 2023;13(1):6533.

12. Iso H, Hennekens CH, Stampfer MJ, et al. Prospective study of aspirin use and risk of stroke in women. Stroke. 1999;30(9):1764-71.

13. Weng JC, Wang J, Du X, et al. Safety of Aspirin Use in Patients With Stroke and Small Unruptured Aneurysms. Neurology. 2021;96(1):e19-e29.

14. Hasan DM, Mahaney KB, Brown RD, Jr., et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke. 2011;42(11):3156-62.

15. Can A, Rudy RF, Castro VM, et al. Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study. Neurology. 2018;91(12):e1175-e81.

16. Shimizu K, Imamura H, Tani S, et al. Candidate drugs for preventive treatment of unruptured intracranial aneurysms: A cross-sectional study. PLoS One. 2021;16(2):e0246865.

17. Chalouhi N, Starke RM, Correa T, et al. Differential Sex Response to Aspirin in Decreasing Aneurysm Rupture in Humans and Mice. Hypertension. 2016;68(2):411-7.

18. Starke RM, Chalouhi N, Ding D, et al. Potential role of aspirin in the prevention of aneurysmal subarachnoid hemorrhage. Cerebrovasc Dis. 2015;39(5-6):332-42.

19. Chalouhi N, Jabbour P, Starke RM, et al. Aspirin for prophylaxis against cerebral aneurysm rupture. World Neurosurg. 2014;81(1):e2-3.

20. Hasan DM, Bayman E, Broderick J. Letter by Hasan et al Regarding Article, "Aspirin and Risk of Subarachnoid Hemorrhage: Systematic Review and Meta-Analysis". Stroke. 48. United States2017. p. e184-e5.

21. Shanahan RM, Hudson JS, Hasan DM. Response to: Aspirin and Subarachnoid Haemorrhage in the UK Biobank. Transl Stroke Res. 15. United States2024. p. 863-4.

22. Vergouwen MD, Rinkel GJ, Algra A, et al. Prospective Randomized Open-label Trial to evaluate risk faCTor management in patients with Unruptured intracranial aneurysms: Study protocol. Int J Stroke. 2018;13(9):992-8.

23. Hall S, Birks J, Anderson I, et al. Risk of Aneurysm Rupture (ROAR) study: protocol for a long-term, longitudinal, UK multicentre study of unruptured intracranial aneurysms. BMJ Open. 2023;13(3):e070504.

24. Demirci B, Demir O, Dost T, et al. Antioxidative effect of aspirin on vascular function of aged ovariectomized rats. Age (Dordr). 2014;36(1):223-9.

**Figure Legends**

Figure 1. Kaplan–Meier plot comparing the rates of SAH in participants reporting on acetylsalicylic acid use.

Figure 2. Kaplan Meier plot comparing the rates of SAH for acetylsalicylic acid dose categories.

Figure 3. Kaplan Meier plot comparing the rates of SAH for acetylsalicylic acid frequency categories.

**Tables**

Table 1. Multivariate survival analysis comparing the relationship between acetylsalicylic acid subgroups and SAH.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HR** | **95% confidence interval** | **p-value** |
| **Lower CI** | **Upper CI** |
| **Acetylsalicylic acid use** | **SAH** | 1.02 | 0.82 | 1.28 | 0.85 |
| **Aneurysmal SAH** | 1.04 | 0.78 | 1.39 | 0.78 |
| **Idiopathic SAH** | 0.94 | 0.65 | 1.34 | 0.72 |
| **Fatal SAH** | 0.99 | 0.73 | 1.35 | 0.97 |
| **Non-Fatal SAH** | 1.05 | 0.77 | 1.43 | 0.75 |
| **Acetylsalicylic acid dose** | **SAH** | 1.03 | 1.00 | 1.06 | 0.02 |
| **Aneurysmal SAH** | 1.03 | 1.00 | 1.07 | 0.08 |
| **Idiopathic SAH** | 1.04 | 1.00 | 1.08 | 0.07 |
| **Fatal SAH** | 1.04 | 1.00 | 1.08 | 0.03 |
| **Non-Fatal SAH** | 1.02 | 0.98 | 1.06 | 0.32 |
| **Acetylsalicylic acid frequency** | **SAH** | 1.06 | 0.99 | 1.13 | 0.07 |
| **Aneurysmal SAH** | 1.03 | 0.94 | 1.13 | 0.49 |
| **Idiopathic SAH** | 1.11 | 1.00 | 1.23 | <0.05 |
| **Fatal SAH** | 1.09 | 0.99 | 1.20 | 0.07 |
| **Non-Fatal SAH** | 1.03 | 0.95 | 1.13 | 0.46 |
| **Acetylsalicylic acid duration** | **SAH** | 1.00 | 0.99 | 1.01 | 0.80 |
| **Aneurysmal SAH** | 1.00 | 0.99 | 1.02 | 0.56 |
| **Idiopathic SAH** | 1.00 | 0.98 | 1.01 | 0.98 |
| **Fatal SAH** | 1.00 | 0.99 | 1.02 | 0.59 |
| **Non-Fatal SAH** | 1.00 | 0.98 | 1.02 | 0.86 |

Table 2. Multivariate survival analysis comparing the relationship between acetylsalicylic acid dose and SAH.

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose** | **HR** | **95% confidence interval** | **P value** |
| **Lower** | **Upper** |
| **SAH** | **Past use** | 0.82 | 0.59 | 1.15 | 0.26 |
| **1-2 tabs/ week** | 0.69 | 0.48 | 1.00 | 0.05 |
| **3-5 tabs/ week** | 1.02 | 0.66 | 1.57 | 0.92 |
| **6-14 tabs/ week** | 1.07 | 0.70 | 1.62 | 0.76 |
| **15+ tabs/week** | 1.34 | 0.83 | 2.18 | 0.23 |
| **Current, unknown dose** | 0.95 | 0.52 | 1.73 | 0.86 |
| **Non-fatal** | **Past use** | 0.71 | 0.45 | 1.14 | 0.16 |
| **1-2 tabs/ week** | 0.73 | 0.45 | 1.19 | 0.21 |
| **3-5 tabs/ week** | 0.91 | 0.49 | 1.68 | 0.76 |
| **6-14 tabs/ week** | 0.79 | 0.42 | 1.48 | 0.47 |
| **15+ tabs/week** | 1.33 | 0.67 | 2.63 | 0.41 |
| **Current, unknown dose** | 0.99 | 0.43 | 2.27 | 0.97 |
| **Fatal** | **Past use** | 0.95 | 0.59 | 1.54 | 0.84 |
| **1-2 tabs/ week** | 0.65 | 0.37 | 1.13 | 0.13 |
| **3-5 tabs/ week** | 1.15 | 0.63 | 2.10 | 0.64 |
| **6-14 tabs/ week** | 1.36 | 0.78 | 2.38 | 0.28 |
| **15+ tabs/week** | 1.37 | 0.69 | 2.74 | 0.37 |
| **Current, unknown dose** | 0.91 | 0.37 | 2.26 | 0.84 |
| **Aneurysmal** | **Past use** | 0.78 | 0.50 | 1.22 | 0.27 |
| **1-2 tabs/ week** | 0.75 | 0.47 | 1.21 | 0.24 |
| **3-5 tabs/ week** | 0.99 | 0.57 | 1.76 | 0.99 |
| **6-14 tabs/ week** | 0.94 | 0.53 | 1.64 | 0.82 |
| **15+ tabs/week** | 1.21 | 0.63 | 2.31 | 0.57 |
| **Current, unknown dose** | 0.93 | 0.41 | 2.13 | 0.86 |
| **Idiopathic** | **Past use** | 0.98 | 0.57 | 1.68 | 0.94 |
| **1-2 tabs/ week** | 0.57 | 0.30 | 1.07 | 0.08 |
| **3-5 tabs/ week** | 1.12 | 0.56 | 2.27 | 0.75 |
| **6-14 tabs/ week** | 1.30 | 0.68 | 2.47 | 0.43 |
| **15+ tabs/week** | 1.64 | 0.76 | 3.53 | 0.21 |
| **Current, unknown dose** | 1.09 | 0.42 | 2.82 | 0.86 |