Sex and age effects on risk of non-traumatic subarachnoid hemorrhage: Retrospective cohort study of 124,234 cases using electronic health records

Charlotte H Harrison, MRCP,[a] Maxime Taquet, PhD,[b,c] Paul J Harrison, FRCPsych,[b,c] Peter J Watkinson, MD,[a,d,e] and Matthew J Rowland, PhD[a]

Objectives: The epidemiology of non-traumatic subarachnoid hemorrhage (SAH) is unclear. This study describes the antecedent characteristics of SAH patients, compares the risk of SAH between women and men, and explores if this changes with age. *Materials and methods:* Retrospective cohort study using an electronic health records network based in the USA (TriNetX). All patients aged 18-90y with at least one healthcare visit were included. Antecedent characteristics of SAH patients (ICD-10 code I60) were measured. The incidence proportion and the relative risk between women and men, were estimated overall, in the 55-90y age group, and in five-year age categories. *Results:* Of 58.9 million eligible patients, with 190.8 million person-years of observations, 124,234 (0.21%; 63,467 female, 60,671 male) had a first SAH, with a mean age of 56.8 (S.D. 16.8) y (women: 58.2 [16.2] y, men 55.3 [17.2] y). 9,758 SAH cases (7.8%) occurred in people aged 18-30y. Prior to the SAH, an intracranial aneurysm had been diagnosed in 4.1% (women: 5.8% men: 2.5%), hypertension in 25.1% and nicotine dependence in 9.1%. Overall, women had a lower risk of SAH compared to men (RR 0.83, 95% CI 0.83-0.84), with a progressive increase in risk ratio across age groups: from RR 0.36 (0.35-0.37) in people aged 18-24y, to RR 1.07 (1.01-1.13) aged 85-90y. *Conclusions:* Men are at greater risk of SAH than women overall, driven by younger adult age groups. Women are at greater risk than men only in the over 75-year age groups. The excess of SAH in young men merits investigation.

Keywords: Stroke—Subarachnoid hemorrhage—Epidemiology—Electronic health records

Abbreviations: SAH, Subarachnoid hemorrhage; EHR, Electronic health record

From the [a]Kadoorie Centre for Critical Care Research and Education, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK; [b]Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; [c]Oxford Health NHS Foundation Trust, Oxford, UK; [d]Oxford Critical Care, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; and [e]National Institute for Health and Care Research (NIHR) Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

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Corresponding author at: Kadoorie Centre for Critical Care Research and Education, John Radcliffe Hospital, Oxford OX3 9DU, UK. E-mails: charlotte.harrison@ndcn.ox.ac.uk, mtaquet@gmail.com, paul.harrison@psych.ox.ac.uk, peter.watkinson@ndcn.ox.ac.uk, matthew.rowland@ndcn.ox.ac.uk.

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Introduction

Spontaneous subarachnoid hemorrhage (SAH) accounts for about 5% of strokes, with about 85% attributable to an intracranial aneurysm.[1] Compared to other forms of stroke, SAH affects younger people and has a higher morbidity and mortality.[2] Established risk factors for SAH include family history, hypertension, smoking, and heavy alcohol intake, and a pre-existing intracranial aneurysm.[3-8]

Sex is also often considered to be a risk factor,[9] with women believed to be at greater risk of SAH than men, as shown by a meta-analysis of prospective population-based studies (relative risk 1.24, 95% confidence interval 1.09-1.42;[10]), as well as from other register and cohort studies.[7,11,12] However, the evidence for sex differences in incidence of SAH is nuanced. In an updated meta-analysis, the confidence intervals were broad and included 1 (risk ratio 1.30, 95% CI 0.98-1.70) precluding firm conclusions.[13] Complicating the issue, sex differences in SAH incidence may interact with age, as well as with factors such as smoking and geographical region. For example, de Rooij et al found that sex differences began at age 55,[10] but others have found a different trajectory, with Vyas et al reporting an 'inverted-U' relationship.[12] Regarding smoking, the sex difference is reportedly smaller[7] if not absent[8] in non-smokers. Sex differences also show geographic variation, being prominent in Japan but absent in Europe.[13] Moreover, with regard to age, it is worth noting that all studies to date have had limited numbers of young adults (e.g. 1,063 SAH cases aged 40 or less in Koffijberg et al,[11] and 266 SAH cases aged 35 or less in Lindekleiv et al[7]). Overall, the nature and magnitude of sex differences in SAH risk requires further investigation.

Aims

The aim of this study was to explore the antecedent characteristics of patients who experience an SAH, with particular reference to the question of sex differences across the lifespan. To do so we used an electronic health records network (EHR).

Methods

Our protocol was pre-registered[14] and the study is reported in line with STROBE/RECORD guidelines.[15]

The TriNetX analytics electronic health records network

A retrospective cohort study was performed, using EHR data from the TriNetX Analytics Network ("TriNetX"; www.trinetx.com).

TriNetX is a federated cloud-based network providing access to anonymized, patient-specific EHRs of approximately 80 million patients from 59 healthcare organizations (HCOs) mainly (~96%) located in the USA. The remaining sites include India, Australia, Taiwan, Spain, UK, Bulgaria, and Malaysia. HCOs include hospitals, primary care and specialty treatment providers. A typical HCO is a large academic health center with data coming from the majority of its affiliates. There are on average 26 facilities per HCO. 68% of HCOs provide inpatient and outpatient data, 22% report inpatient data only and 10% provide outpatient data only. HCOs refresh their data on average every 24 days.[16] TriNetX includes insured and uninsured patients, although the proportions of each are unknown. Available data include demographics, diagnoses (ICD-10 codes), interventions, medications, laboratory values and vital signs. Further details about TriNetX can be found in recently published studies.[16-19]

TriNetX complies with the Health Insurance Portability and Accountability Act (HIPAA). This US federal law protects the privacy and security of healthcare data. TriNetX is certified to the ISO 27001:2013 standard. TriNetX upholds an Information Security Management System to protect the healthcare data it has access to and meet the HIPAA Security Rule requirements. All data displayed in the TriNetX Platform is de-identified as per Section §164.514(a) of the HIPAA Privacy Rule. The data de-identification process is verified through formal determination by a qualified expert, as specified in Section §164.514(b)(1) of the HIPAA Privacy Rule.

Each participating HCO represents and warrants that it has all necessary rights, consents, approvals and authority to provide the data to TriNetX under a Business Associate Agreement, so long as their name remains anonymous as a data source and their data are utilized for research purposes. The data shared through the TriNetX Platform are attenuated to ensure that they do not include sufficient information to facilitate the determination of which HCO contributed which specific information about a patient. These protections mean that no ethical approval was required to conduct this study.

Data on demographics (such as age, sex, race) are coded in TriNetX to HL7 version 3 administrative standards. Diagnoses are mapped to ICD-10 codes. Medications are coded to RxNorm and organized by NDF-RT (National Drug File – Reference Terminology). Laboratory results and vital signs are coded to LOINC (Logical Observations Identifiers Names and Codes).

The SAH cohort

A cohort of patients was identified who had suffered a first recorded non-traumatic SAH (ICD-10 code: I60) aged 18-90 years. Demographics (age, sex, race) and relevant lifetime diagnoses (e.g., hypertension, unruptured intracranial aneurysm, nicotine dependence, alcohol use disorders) were captured, as well as medications (e.g., antihypertensives and anticoagulants) and lab values (e.g., blood pressure) recorded in the preceding year. For details of codes and timelines of data capture, see Supplemental Table 1.

Statistical analysis

The incidence proportion was defined as the ratio of first diagnosis of SAH occurring in the given age interval, over the number of people who had at least one healthcare visit within the given age interval. The latter ensures patients were using HCOs within the TriNetX network.

The incidence of SAH in women versus men was compared using risk ratios (RR). The RR was calculated as the ratio of the incidence proportion of SAH in women versus men, with 95% confidence intervals. Risk ratios were calculated as female: male. 95% confidence intervals were calculated using the log transform.[20]

RRs were calculated for the whole cohort, for patients aged 55-90y (as a proxy for the post-menopausal period, as per earlier studies[10]), and in 5-year intervals from 18 to 90 y (with the first interval including 7 years from 18 to 24). To minimize the possibility that findings regarding sex were driven by sex differences in the number of patients well enough not to require a healthcare visit, we performed a sensitivity analysis in which patients within the network who did not have a healthcare visit during the given age interval were included in the denominator of incidence proportion. For a schematic of the analyses, see Supplemental Figure 1. Full details of queries, cohorts and calculation of person-years can be found in the Supplemental Material.

Results

In an EHR network with 59.6 million patients aged 18-90y, with 190.8 million person-years of observations, 124,234 cases of first SAH were recorded. Over 80% of the diagnoses were made from 2012 onwards (likely due to the growth of the network in the past decade). About 50% of data are from HCOs in the southern USA, 45% from other parts of the USA, and 5% from other countries.

Table 1 lists the baseline demographics and antecedent characteristics of the whole cohort of patients with a recorded SAH, and in women and men separately. Of the established risk factors for SAH, pre-existing intracranial aneurysms were diagnosed in 4.1%, hypertension in 25.1%, nicotine dependence in 9.1%, and alcohol-related disorders in 4.7%. Several of these factors showed significant differences between women and men with SAH, notably in the incidence of intracranial aneurysms (2.3x

Table 1. *Baseline demographics and antecedent characteristics of SAH cases*

		Patients with SAH, aged 18-90			Female vs male
		All	Female	Male	
n		124234	63467	60671	
Age at SAH, mean (SD)		56.8 (16.8)	58.2 (16.2)	55.3 (17.2)	t=30.0, p<0.0001
Race %, (n)	White	66.1 (60671)	65.3 (41414)	67.0 (40644)	chi^2=41.8, p<0.00001
	Black or African American	13.5 (16795)	14.0 (8855)	13.1 (7939)	chi^2=19.9, p<0.00001
	Asian	2.2 (2771)	2.4 (1498)	2.1 (1273)	chi^2=9.8, p<0.002
	Unknown	17.7 (22022)	18.0 (11402)	17.4 (10531)	chi^2=41.8, p<0.00001
Hypertension %, (n)		25.1 (31130)	25.0 (15825)	25.2 (15293)	chi^2=1.2, p=0.27
Ischemic heart disease %, (n)		10.1 (12527)	8.3 (5255)	12.0 (7266)	chi^2=467.3, p<0.00001
Diabetes %, (n)		10.5 (13017)	9.9 (6263)	11.1 (6749)	chi^2=52.1, p<0.00001
Unruptured intracranial aneurysm %, (n)		4.1 (5142)	5.8 (3652)	2.5 (1488)	chi^2=851.9, p<0.00001
Nicotine dependence %, (n)		9.1 (11255)	8.1 (5158)	10.0 (6096)	chi^2=41.8, p<0.00001
Alcohol related disorders %, (n)		4.7 (5810)	2.4 (1506)	7.1 (4303)	chi^2=1549, p<0.00001
SBP, mmHG (SD) [% of cohort]		133 (23.5) [30]	133 (23.8) [30]	133 (23.1) [30]	t=0, p=0.99
DBP, mmHG (SD) [% of cohort]		76.1 (14.1) [32]	75.3 (14.1) [32]	77 (13.9) [32]	t=11.7, p<0.0001
Body Mass Index (SD) [% of cohort]		28.2 (6.7) [23]	28.5 (7.2) [23]	27.8 (6.0) [23]	t=8.7, p<0.003
Cholesterol, mmol/l (SD) [% of cohort]		4.34 (1.27) [12]	4.58 (1.24) [12]	4.09 (1.25) [12]	t=24.0, p<0.0001
Anticoagulants %, (n)		16.0 (19871)	14.8 (9424)	17.2 (10436)	chi^2=127.7, p<0.00001
Antiplatelets %, (n)		11.8 (14652)	11.5 (7315)	12.1 (7329)	chi^2=9.2, p<0.003
ACE inhibitors %, (n)		8.7 (10784)	7.9 (5035)	9.5 (5745)	chi^2=92.3, p<0.00001
Angiotensin receptor blockers %, (n)		4.4 (5505)	4.8 (3052)	4.0 (2450)	chi^2=43.5, p<0.00001
Beta-blockers %, (n)		18.9 (23478)	18.1 (11495)	19.7 (11968)	chi^2=52.7, p<0.00001
Calcium channel blockers %, (n)		11.6 (14435)	12.0 (7631)	11.2 (6793)	chi^2=20.7, p<0.00001
Diuretics %, (n)		13.4 (16679)	13.8 (8779)	13.0 (7895)	chi^2=17.9, p<0.00003
Estrogens %, (n)		0.8 (1045)	1.6 (1027)	0.0 (10)[a]	n/a
Other antihypertensives %, (n)		11.2 (13968)	10.2 (6502)	12.3 (7461)	chi^2=131.1, p<0.00001

Diagnoses recorded at any time prior to SAH; lab values and medication data refer to the year prior to the SAH. Numbers in square brackets are the percentage of patients who had a value recorded during that time. SBP: systolic blood pressure. DBP: diastolic blood pressure. SD: standard deviation.

[a]To preserve anonymity, TriNetX returns a value of 10 if there are less than 10 observations.

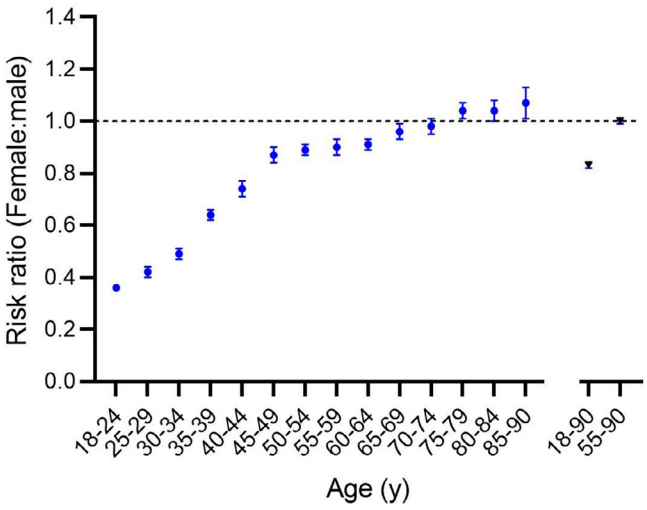

Fig. 1. *Risk ratio (female:male) of SAH in 5-year age groups. Summary statistics for 18-90y and 55-90y age groups shown on right hand side.*

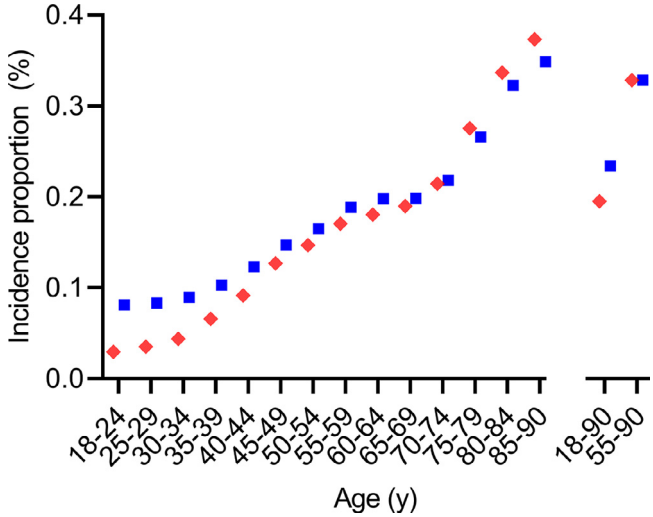

Fig. 2. *Incidence proportion in women (diamond) and men (square) in 5-year age groups. Summary statistics for 18-90y and 55-90y age groups on right hand side.*

more common in women), nicotine dependence (1.2x more common in men) and alcohol-related disorders (3x more common in men).

The numbers of patients in each 5-year age group are shown in Supplementary Table 2; of note, there are at least 2,900 people with SAH in each age group, including 1809 women and 3432 men aged 18-24 y.

In the whole cohort, the RR of SAH in women versus men was 0.83 (95% CI, 0.83-0.84). Fig. 1 shows the RR in each 5-year group, as well as for those aged 55-90 y. There was a consistent increase in RR in each 5-year age group, increasing from RR=0.36 (0.35-0.37) in people aged 18-24y, to RR=1.07 (1.01-1.13) in those aged 85-90y. The RR for those aged over 55y was 1.0 (0.99-1.01). A sensitivity analysis that included patients without a healthcare visit showed similar results (Supplementary Figure 2).

The incidence proportions for both sexes in each age category are shown in Fig. 2, and show a steady increase with age, with no plateau and the highest incidence proportion in the most elderly groups.

Discussion

Using a large EHR network, we report on the antecedent characteristics of almost 125,000 cases of SAH. The main strength of this study is its size, which compares to a total of 8,173 SAH cases in a recent meta-analysis,[13] and the largest register study, which had 18,443 SAH episodes.[11] Therefore, our results are relatively robust, with tighter confidence intervals and greater precision. Furthermore, our data are, to our knowledge, the first large-scale SAH data predominantly from the USA, with the majority of previous studies being in Scandinavian or Asian populations. This focus on a single geographical region limits generalizability of results to other countries, but markedly reduces the heterogeneity that arises from the different SAH incidences and risk factors seen in different countries and populations. The fact that approximately 20% of the total US population is included in the TriNetX network implies that generalizability *within* the USA is likely to be adequate. Similarly, since over 80% of all SAH diagnoses in the EHR network were made from 2012 onwards, a possible decline in SAH over time, as has been suggested in earlier studies,[13] is unlikely to be a major confounder.

Several of our findings are consistent with the previous literature, such as the mean age for SAH of 62 years,[2,9] and the percentage of people with SAH who have a history of unruptured aneurysm (4.1% overall, with a higher proportion (5.8%) amongst women), which compares to 3.2% and a prevalence amongst women of 6%, in a meta-analysis.[3] The age distribution of SAH has been less clear in terms of whether it peaks in the sixth decade or continues rising into old age; our data support the latter finding.

We find an overall higher incidence of SAH in men than women. This is in contrast with the literature, which reports significant or trend differences in the opposite direction.[10-13] A likely explanation is that our study covers younger age groups typically not included in other studies. Indeed, the discrepancy almost entirely relates to young adults, in whom we find a clear excess in men, whereas our results from the seventh decade onwards show either equal sex incidence, or a female predominance, depending on how the age categories are divided. In this study, we included 9,758 SAH cases aged less than 30, and 21,277 aged less than 40 years old. By contrast, previous studies that have reported on SAH in these age groups typically have at most a few hundred cases, and the Etminan et al meta-analysis of age-by-sex risks only had 2,133 SAH cases altogether.[13] Given that our results

are otherwise in line with the rest of the literature in age groups that have been well investigated, a reasonable conclusion is that our data fill a gap in the literature, rather than contradict it.

There are several limitations of analyses based on data from health records (compared to prospective population studies or studies based on dedicated registers). Limitations include: (1) diagnoses are not validated. However, using the I60 code to identify SAH cases in health records has a positive predictive value of 0.96,[21] suggesting this is not a major source of bias. (2) Patients may also receive healthcare from HCOs not in the network, leading to missing data. (3) TriNetX has accurate mortality data for death that occurs within an HCO (e.g., in-hospital death) and regularly imports death status from third-party organizations for a subset of individuals. However, some cases of sudden death from SAH occurring outside an HCO might be missed and the diagnosis of SAH might not be retrospectively recorded after death. Lindbohm et al found that women were more likely to suffer sudden death from SAH than men, which may contribute to the differences in results.[8] (4) The use of retrospective health records data precludes calculation of total follow-up time and so our incidence data cannot be directly compared to prospective cohort or population-based studies. (5) Some factors relevant to SAH risk could not be ascertained, such as family history, current smoking, current alcohol intake and recreational drug use. (6) We focus on non-traumatic subarachnoid hemorrhage (I60) as an overarching diagnosis, and do not distinguish between aneurysmal and non-aneurysmal SAH. The different etiologies of SAH are associated with differing morbidity and mortality,[2,9] and may be associated with different patterns of sex difference. For further discussion of the uses and limitations of EHRs for observational research, see.[22,23]

These factors together mean that the present results should be interpreted with caution, notwithstanding the size of the sample, and viewed in conjunction with the findings from other study designs. On the other hand, it is difficult to envisage how these limitations could have produced the age-by-sex effects on SAH incidence, since the various sources of error and bias would likely affect both sexes, and all age groups, to a similar extent. As such, the apparently greater risk of SAH in young men than young women merits explanation. Current theories to explain sex differences in SAH include hormonal factors,[24–27] and a differential impact of smoking.[8] However, these theories were proposed in order to explain an excess of SAH in older females and may not be relevant to the opposing direction of effect in younger men.

In summary, we have used EHRs to report the characteristics of 124,234 people diagnosed with a first spontaneous SAH and describe how the incidence varies with age and sex. Unexpectedly, we found a higher risk in men than women, which can be explained by cases recorded in younger adult age groups, with women only predominating in old age. While statistically robust, these findings need to be interpreted cautiously and replicated in other datasets given the limitations of EHR data. If confirmed, the higher risk of SAH in younger men merits further investigations to identify etiological factors and possibly propose strategies to mitigate those risks.

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Contributions

CHH, MT, MJR, PJH and PW conceived the study design. CHH completed the analysis with support from MT and MJR. MT assisted with data acquisition, analyses, and interpretation. CHH wrote the manuscript, and all authors contributed to and provided approval for the submitted version.

Data Availability

CHH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. TriNetX will grant access to researchers if they have a specific concern (through a third-party agreement option).

Declaration of Competing Interest

PW holds grants from the NIHR, Wellcome and Sensyne Health (now Arcturis Data). He was previously Chief Medical Officer for Sensyne Health and holds shares in the company. He provides consultancy for Arcturis Health. He sits on the NIHR Invention for Innovation (i4i) Product Development Award Panel. MJR declares grants from the UK NIHR. He is currently an employee of Novartis International. CHH, MT and PJH have no conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2023.107196.

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