Sex differences in
Aneurysmal Subarachnoid Haemorrhage

by

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(Medical Studies)

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Declaration of originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by any other person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human experimentation, and the rulings of the Safety, Ethics, and Institutional Biosafety Committees of the University.

The study ReDucing Delays In aneurysmal Subarachnoid Haemorrhage (REDDISH; Chapters 4 and 5) comprising of a retrospective cohort study of patients with aSAH was approved by the Human Research Ethics Committee in Victoria (RES-18-0000-036A) and Tasmania (H0014563). Appropriate ethics and/or governance approvals were obtained from the Australian Institute of Health and Welfare (AIHW) to conduct data linkage to the National Death Index (NDI).

The research using the pooling data from 13 population-based studies forming the INternational STroke oUtCome sTudy (INSTRUCT; Chapter 6) was approved by the Tasmanian Health and Medical Human Research Ethics Committee; reference number is H0014861. All the participating studies had signed informed consent and approval from their respective local Ethics Committees.

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Statement of Co-Authorship

This thesis includes work which has been published, submitted, or ready for publication in peer-reviewed journals. Publication/manuscript details for each Chapter are described in the "Publications arising from the thesis" section.

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Rehman S, Sahle BW, Chandra RV, Dwyer M, Thrift AG, Callisaya M, et al. Sex differences in risk factors for aneurysmal subarachnoid haemorrhage: Systematic review and meta-analysis. *Journal of the neurological sciences*. 2019;406:116446

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Paper 2: Sex Differences in Aneurysmal Subarachnoid Haemorrhage (aSAH): Aneurysm characteristics, Neurological complications, and Outcome

Located in Chapter 4

Rehman S, Chandra RV, Zhou K, Tan D, Lai L, Asadi H, et al. Sex differences in aneurysmal subarachnoid haemorrhage (asah): Aneurysm characteristics, neurological complications, and outcome. *Acta Neurochirurgica*. 2020;162:2271-2282
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Paper 3: Adherence to evidence-based processes of care reduces one-year mortality after Aneurysmal Subarachnoid haemorrhage (aSAH)

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Paper 4: Sex differences in short and long-term mortality and functional outcome after subarachnoid haemorrhage (SAH) in INternational STRoke oUtComes sTudy (INSTRUCT)-Pooled analysis of the individual participant data

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Thesis Abstract

Background: Aneurysmal subarachnoid haemorrhage (aSAH) has a greater incidence in women compared to men. Few studies have explored if sex differences in risk factors for aSAH contribute to this disparity. Similarly, very few authors examined sex differences in long and short-term outcomes and there are inconsistent findings reported among the studies that have been conducted. Therefore, there is a need for high-quality studies to examine sex differences in the risk factors and the outcomes of aSAH. Such findings will be useful to devise sex-specific interventions to improve the prevention, management, and outcome of aSAH.

Aims: (1) Examine sex differences in the risk factors for aSAH; (2) examine sex differences in the short and long-term outcomes after aSAH; and (3) identify factors that explain sex differences in poor outcomes after aSAH.

Methods: This thesis contains four chapters presenting studies addressing these aims.

Chapter 3: A systematic review and meta-analysis to examine sex differences in risk factors for aSAH. I included case-control and cohort studies based on sex differences in the risk factors for aSAH published up to 2017. Random-effects meta-analysis was used to pool estimates for a risk factor in men and women by approximating odds ratio (OR) and risk ratios (RR) when a risk factor was reported in ≥ 2 studies.

Chapter 4 and chapter 5: Data were from REDucing Delays In aneurysmal Subarachnoid Haemorrhage (REDDISH) study, comprising of a retrospective cohort of all patients diagnosed with aSAH across two large public healthcare networks in Australia between 2010-2016. Multiple overlapping sources were used to identify the potential cases of aSAH with data extracted from medical records by trained research assistants. Study factors include sex, demographics, social factors, aneurysm characteristics, neurological complications, and clinical management. Outcome after aSAH were (1) discharge destination (home vs rehabilitation and death) after acute hospital admission; and (2) survival up to 1 year or (3) causes of death up to 1 year obtained by data linkage to the National Death Index (NDI). The REDDISH study was used to examine sex differences in neurological complications, aneurysm characteristics, and outcomes. This data source was also used to examine sex differences in adherence to evidence-based processes of care after aSAH, 1-year mortality and causes of death, including if these differed by sex.

Chapter 6: Data were from the International Stroke Outcomes Study (INSTRUCT). This study is a collaboration between investigators for 13 high quality population-based stroke incidence studies from Australasia, Asia, Europe, South America, and the Caribbean between 1993-2017. De-identified individual participant data was harmonised on sociodemographic factors, health behaviours, pre-stroke comorbidities, the severity of stroke and outcomes of (1) mortality at 30 days, 1 year, and 5 years and (2) poor functional outcome at 30 days, 1 year, and 5 years. This dataset was used to examine sex differences in the prevalence and predictors of short and long-term outcomes after SAH, including mortality and functional outcomes at 30 days, 1 year and 5 years.

Results:

Chapter 3: There were 31 studies (27 case-control and 4 cohort) identified. Female sex was associated with greater likelihood of aSAH. There was no detectable difference between the sexes for common risk factors like hypertension, smoking, aSAH family history, systolic blood pressure, age, and some genetic variations. Alcohol, high alanine aminotransferase (ALT) levels, and some gene variants increased the risk of aSAH in men. Reproductive factors, divorce and some genetic variations increased the risk in women. High aspartate aminotransferase (AST) levels in men and, diabetes and parity in women reduced the risk of aSAH.

Chapter 4: There were a total of 577 patients with aSAH included and women were over-represented compared to men (69% vs 31%). Mean aneurysm size was greater in men than women. Delayed cerebral ischaemia (DCI) and hydrocephalus were more common neurological complications in women than men. Pre-stroke confounders including age, hypertension history, smoking status, and neurological complications (DCI and hydrocephalus) explained the slightly greater risk of poor outcomes in women after acute admission.

Chapter 5: There were 549 patients with aSAH included in this study from the REDDISH dataset. Approximately 60% were managed according to the treatment guidelines, with no sex differences noted. Individual indicators of care were associated with improved survival up to 1 year. Optimal care reduced mortality at 1 year independent of age, sex, severity, comorbidities, and hospital network.

Chapter 6: There were 657 patients with SAH (46% men) in the INSTRUCT study. There was limited evidence of sex differences in mortality and poor functional outcome at 30 days, 1 year

and 5 years. Poor outcomes were associated with non-modifiable factors including age and severity of the stroke, but also risk factors that predict SAH incidence including smoking.

Conclusion: Despite the over-representation of women in cohorts with aSAH, there were no striking differences between men and women in the risk factors and outcomes examined in this thesis. Most established risk factors (e.g. hypertension and smoking) are equally a risk for aSAH in men and women. However, the role of hormonal risk factors needs further exploration as these may assist in the prevention and management of aneurysmal rupture in both men and women. Men and women mostly had the same survival and functional outcomes in the short and long term after aSAH. Women more often suffered complications like DCI and hydrocephalus than men. Across analyses, outcomes after aSAH were mostly associated with modifiable risk factors for aSAH incidence (e.g. smoking or hypertension) but also non-modifiable risk factors such as age and severity of stroke. Thus, devising better strategies for prevention and management of risk factors for aSAH, ensuring evidence-based care for aSAH is provided to all patients, and improving management of neurological complications could help improve the outcomes after aSAH for men and women.

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List of Publications

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Rehman S, Chandra RV, Zhou K, Tan D, Lai L, Asadi H, Froelich J, Thani N, Nichols L, Blizzard L, Smith K, Thrift AG, Stirling C, Callisaya ML, Breslin M, Reeves MJ, Gall S. Adherence to evidence-based processes of care reduces one-year mortality after Aneurysmal Subarachnoid haemorrhage (aSAH)**.** *At the time of submission of this thesis, the contents of the manuscript (in Chapter 5) were submitted to the International Journal of Stroke*

Rehman S, Phan HT, Reeves MJ, Thrift AG, Cadilhac DA, Jonathan Sturm, Breslin M, Callisaya ML, Vemmos K, Parma P, Krishnamurthi R, Barker-Collo S, Feigin V, Chausson N, Olindo S, Cabral NL, Carolei A, Marini C, Sacco S, Correia M, Appelros P, Kõrv J, Vibo R, Minelli C, Sposato L, Pandian JD, Kaur P, Azarpazhooh MR, Morovatdar N, Gall S. Sex differences in short and long-term mortality and functional outcome after subarachnoid haemorrhage (SAH) in INternational STRoke oUtComes sTudy (INSTRUCT)-A pooled analysis of the individual participant data. *At the time of submission of this thesis, the contents of this manuscript (in Chapter 6) have been circulated to co-authors in preparation for submission for publication.*

Manuscripts published during candidature, but external to thesis material

Dwyer M, Rehman S, Ottavia T, Stankovich J, Gall S, Peterson G, Karen Ford K, Kinsman L. Urban-rural differences in the care and outcomes of acute stroke patients: Systematic review. *J Neurol Sci*. 2019; 397: 63-74

Published abstracts

1. **Rehman S**, Sahle B, Chandra RV, Dwyer M, Thrift AG, Callisaya M, Breslin M, Phan HP, Otahal P and Gall S. Abstract WMP58: Sex Differences in Risk Factors for Aneurysmal Subarachnoid Hemorrhage: Systematic Review and Meta-Analysis. *Stroke* 2019;50: AWMP58-AWMP58

2. **Rehman S**, Sahle B, Chandra RV, Dwyer M, Thrift AG, Callisaya M, Breslin M, Phan HP, Otahal P and Gall S. Abstract wp237: Risk factors for aneurysmal subarachnoid hemorrhage in women: Systematic review and meta-analysis. *Stroke*. 2019;50:AWP237-AWP237

3. **Rehman S**, Chandra RV, Zhou K, Tan D, Lai L, Asadi H, Froelich J, Thani N, Nichols L, Blizzard L, Thrift AG, Stirling C, Breslin M, Callisaya M, Smith K, Stankovich J and Gall S. Sex differences in the characteristics of aneurysms in aSAH and their role in outcome. *Int J Stroke*. 2019;14:27-27

4. **Rehman S**, Chandra RV, Zhou K, Tan D, Lai L, Asadi H, Froelich J, Thani N, Nichols L, Blizzard L, Thrift AG, Stirling C, Breslin M, Callisaya M, Smith K, Stankovich J and Gall S Sex differences in aneurysmal subarachnoid haemorrhage (aSAH): Complications and outcome. *Int J Stroke*. 2019;14:8-8

5. Nguyen TP, **Rehman S**, Chandra R, Zhou K, Tan D, Lai L, Asadi H, Froelich J, Thani N, Nichols L, Blizzard L, Thrift AG, Stirling C and Gall S. Triage category and time to ct in a retrospective cohort of aneurysmal subarachnoid haemorrhage across two tertiary referral networks. *Int J Stroke*. 2019;14:25-25

6. **Rehman S**, Chandra RV, Lai L, Stirling C, Asadi H, Froelich J, Thani N, Nichols L, Blizzard L, Smith K, Breslin M, Reeves M, Callisaya M, Thrift AG, Zhou K, Tan D and Gall S. Sex differences in evidence-based processes of care and one-year survival after aneurysmal subarachnoid hemorrhage (aSAH)-Reddish study. *Int J Stroke*. 2020; 15: 581

Scientific presentations

Presentation at international conferences

- European Stroke Organisation Conference 2020, Virtual (Poster presentation)

- International Stroke Conference 2019, USA (Moderated presentation)

- International Stroke Conference 2019, USA (Poster presentation)

Presentations at domestic conferences

- National Stroke Data Linkage Interest Group Conference 2020, Virtual (Oral presentation)

- Stroke Society of Australasia Conference 2019, Canberra (Oral presentation)

- Stroke Society of Australasia Conference 2019, Canberra (Poster presentation)

- The 12th Graduate Research Conference 2018, UTAS (Poster presentation)

List of Abbreviations

A1	Pre-communicating part of ACA
ACho	Anterior choroidal
ACA	Anterior cerebral artery
Acomm	Anterior communicating artery
ACE	Angiotensin converting enzyme
ACROSS	Australian cooperative research on subarachnoid haemorrhage study
ADAMST13	A Disintegrin-like and Metalloprotease with Thrombospondin Type1 Motif, 13
AF	Atrial fibrillation
AFR	African region
AICA	Anterior inferior cerebellar artery
AMR-US/Can	United States/Canada
AMR-L	American region-Latin America
AHA	American Heart Association
ALT	Alkaline aminotransferase
AST	Aspartate aminotransferase
aSAH	Aneurysmal subarachnoid haemorrhage
AuSCR	Australian Stroke Clinical Registry
AVMs	Arteriovenous malformations
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
DCI	Delayed cerebral ischaemia
DM	Diabetes Mellitus
DSA	Digital subtraction angiography
EBI	Early brain injury
ED	Emergency department
EMR	Eastern Mediterranean region
EQ-5D	European Quality of life

EUR	European region
ETS	Environmental tobacco smoke
EVD	Extra-ventricular drain
FIM	Functional Independence Measure
FXIII	Clotting factor XIII
GBD	Global burden diseases
GCS	Glasgow coma scale
GDHT	Goal Directed Haemodynamic Therapy
GOS	Glasgow outcome scale
Gp	Glycoprotein
GpIIIa	Glycoprotein IIIa
HRQOL	Health Relatd Quality Of Life
HRT/HT	Hormone replacement therapy
HR	Hazard ratio
HTN	Hypertension
ICA	Internal carotid artery
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
I/D	insertion/deletion
IHD	Ischaemic heart disease
IRR	Incidence rate ratio
ISAT	International Subarachnoid Aneurysm Trial
IVH	Intraventricular haemorrhage
MCA	Middle cerebral artery
M1	Sphenoidal segment of MCA
MRA	Magnetic Resonance Angiography
MRR	Mortality rate ratio
mRS	Modified Rankin scale
NEMESIS	North East Melbourne stroke study
NDI	National Death Index
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological disorders
NO	Nitric oxide
NOS	Nitric oxide synthase

OR	Odds ratio
OCPs	Oral contraceptive pills
PCA	Posterior cerebral artery
PCR	Polymerase chain reaction
P1	Pre-communicating part of PCA
P2	Post-communicating part of PCA
PICA	Posterior inferior cerebellar artery
Pcomm	Posterior communicating
PVD	Peripheral vascular disease
RCT	Randomised control trial
REDDISH	REDucing Delays In aneurysmal Subarachnoid Haemorrhage
REDCap	Research Electronic Data Capture
RFLP	Restriction fragment length polymorphism
RR	Risk ratio/Relative risk
RER	Relative excess risk
RRR	Relative risk ratio
SAHIT	Subarachnoid Haemorrhage International Trialists
SBP	Systolic blood pressure
SCA	Superior cerebellar artery
SEAR	South-East Asia region
sHR	Specific hazard ratio
SMR	Standardised mortality ratio
SNP	Single nucleotide polymorphism
TIA	Transient ischaemic attack
TNF	Tumor necrosis factor
UIA	Unruptured intracranial aneurysm
UK	United Kingdom
UN	Urea Nitrogen
V-B junction	Vertebrobasilar junction
VPS	Ventriculo-peritoneal shunt placement
VNTR	Variable number tandem repeat
WFNS	World Federation of Neurosurgical Societies
WHO	World Health Organization
WPR	Western Pacific region

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Chapter 1: Introduction

1.1   Background

Aneurysmal subarachnoid haemorrhage (aSAH) is a type of haemorrhagic stroke.[1] It is a rare type of stroke accounting for around 5% of all cases.[2] A subarachnoid haemorrhage can occur due to trauma,[3] the rupture of intracranial aneurysm, arteriovenous malformation (AVM), coagulation disorders, dissection, cocaine abuse,[4] moyamoya disease, several inherited conditions like Ehler-Danlos Type 4 and autosomal dominant polycystic kidney disease[5], reversible vasoconstriction syndrome[6] and amyloid angiopathy.[7] However, in 85% of the cases, the reason for the bleed is a ruptured intracranial aneurysm.[8] Bleeding from the ruptured aneurysm accumulates in the subarachnoid space. An excruciating headache is a well-known symptom of aSAH with a thunderclap characteristic.[9] Other symptoms include nuchal rigidity, seizures, nausea, vomiting and focal neurological deficits.[10] Around 40% of patients may present with a sentinel headache, which is a warning leak occurring a few weeks before major haemorrhage.[11] About 25-50% of the patients with aSAH will die.[12] However, it is important to note that one in four patients of aSAH die outside hospital setting.[13] Therefore, it is likely that most of the cases of aSAH could not be part of epidemiological studies due to sudden deaths and inclusion of only hospital based cases.[14] The estimated risk of sudden death in aSAH is 12.4% (95% CI 11%-14%).[15] The cost of SAH hospital treatment and rehabilitation is higher compared to ischaemic stroke.[16] Only 30% of the survivors can live independently.[17]

The incidence of aSAH ranges from 4.5-11.2 per 100,000 person-years[18, 19 20, 21] discussed in detail in the later sections. Regarding pathophysiology of this type of stroke, two phases have been noted in the disease's course: early brain injury due to initial bleed (EBI) occurs within 3 days and delayed cerebral ischaemia (DCI) takes place on 4 or 5th days after the onset, reaches peak after 6-8 days and resolves after 12-14 days.[22] During EBI, the extravasated blood leads to headache, rise in intracranial pressure, acute hydrocephalus, cerebral edema, impairment of regional blood flow and autoregulation leading to hypoxia and ischemia, and neuronal degeneration.[22, 23] DCI is a clinical phenomenon that may resolve or progress to cerebral infarction which is diagnosed by imaging.[24] In addition, microthrombosis, cortical spreading depolarization and inflammation are also part of the complex pathophysiology of the disease.[22]While other stroke types that are managed by physicians including neurologists, aSAH/SAH requires management by neurosurgeons or interventional neuroradiologists While

other stroke types that are managed by physicians including neurologists, aSAH/SAH requires mainly a neurosurgical management.[25] This division between the health professional groups that manage aSAH/SAH compared to other stroke types has been one of the limitations of not being included in national stroke registries and therefore resulting in lack of existing evidence on quality of care in this stroke type.

It is important to highlight that throughout this thesis term 'sex' will be used rather than 'gender'. Sex refers to biological or physiological differences between men and women whereas gender refers to socially determined roles of both sexes.[26] As described in detail later in this chapter, women account for around 70% of all cases of aSAH. There appear to be some sex differences in the epidemiology of aSAH, but the reasons for these differences are not well understood. There is a well-developed field of research into sex differences in stroke, particularly ischaemic strokes that account for around 80% of all cases of stroke. Sex differences in care and outcome for people with stroke may exist due to patient-level factors, such as age or comorbidities, but could also reflect gender bias in the provision of care.[27] Understanding if such differences exist, and if they do what might explain them, is important for ensuring equitable outcomes for all people with aSAH. Unfortunately, aSAH is often excluded from the epidemiological or clinical studies used for these analyses, so sex differences in aSAH are under-studied.

The dearth of literature on aSAH has limited our understanding of factors contributing to sex differences in incidence, management, and outcomes. This is therefore the focus of this thesis. The objective of this research is to explore factors contributing to sex differences in incidence, management and outcomes of aSAH. If we know more about sex differences in aSAH then we can facilitate sex-specific preventive care to decrease the incidence of the disease, especially in women. Information on sex differences in risk factors of aSAH could help with prevention. For example, there may be benefits of sex-specific modification of lifestyle for the primary prevention of the disease in people at high risk (e.g. with intracranial aneurysms or a family history of aSAH). We may be able to promote improvement in the outcomes as has been done for other diseases like ischaemic stroke and heart diseases.[28, 29] If differences by sex are observed in the management of aSAH, this could help in devising sex-specific interventions to improve management such as quality improvement programs. Similarly, a difference between women and men in the outcomes after aSAH could help in identifying the health system and individual-level factors that could be targeted to improve outcomes.

This chapter provides an overview of the epidemiology of aSAH including incidence and outcomes, with a focus on what is known and where the gaps in the evidence exist about sex differences in aSAH.

1.2 Incidence of aSAH

1.2.1 Worldwide incidence

The incidence of SAH, or aSAH specifically, has been estimated in several different studies. Systematic reviews and meta-analysis have been conducted with the incidence of SAH, e.g. including aneurysmal and non-aneurysmal causes, estimated in these reviews is summarized in **Table 1-1**.

Table 1-1 Comparison of incidence of SAH in different review studies

Study	Study period	Number of studies	Number of countries	Study designs	Incidence of SAH (95% CI) per 100,000 person-years	Time trends in incidence (Incidence rate ratio [IRR])
Linn et al[18] (1996)	1960-1994	18	12	Prospective population-based	10.5 (9.9-11.2)	0.95* (0.93-0.96)
de Rooij et al[19] (2007)	1960-2005	51	21	Prospective population-based	9.1 (8.8-9.5)	0.99** (0.98-1.00)
Hughes et al[20] (2018)	1990-2016	58	31	Prospective, retrospective, and cross-sectional hospital and population-based	6.67 (4.50-9.25)	-
Etminan et al[21] (2019)	1960-2017	75	32	Prospective population-based	7.9 (6.9-9.0)	-1.7%*** (0.6-2.8)

*Annual decrease in the incidence rate
**Incidence rate decrease in reference region (The United State of America [USA], Australia, New Zealand, Russia, Denmark, Spain, Italy Sweden, United Kingdom [UK], France, Germany, Portugal, Estonia, Kuwait and Georgia) adjusted for age and sex
***Global annual % age decline between 1955-2014

In the review by Hughes et al.[20], the relatively lower incidence of aSAH compared to other reviews could be due to a short study period which starts from 1990 instead of 1960. The incidence of SAH has decreased over the years, which could be attributed to better risk factor management at the population level (e.g. reductions in smoking or hypertension).

1.2.1.1 Geographical variation

Geographical variation has been reported in the incidence of aSAH. The first reviews of geographic variation in the incidence of aSAH or SAH were published in the 1990s. In a review published in 1996, for studies between years 1960-1994, the incidence in Finland was 21.4 (95% CI 19.5 to 23.4) per 100,000 person-years, compared to non-Finnish population-based studies which had an incidence of 7.8 (95% CI, 7.2 to 8.4) per 100,000 person-years.[18] The authors of a systematic review conducted in 2007, which included studies from 1960 to 2005, showed a higher incidence in Japan and Finland compared to 'other' countries, categorized as the reference group (**Figure 1-1**). The reference group included studies from the United States of America (USA), Australia, New Zealand, Russia, Denmark, Spain, Italy Sweden, United Kingdom (UK), France, Germany, Portugal, Estonia, Kuwait and Georgia. The incidence in Japan was 22.7 (95% CI 21.9-23.5) per 100,000 person-years and in Finland was 19.7 (95% CI 18.1-21.3) per 100,000 person-years compared to the reference group with an incidence of 9.1 (95% CI 8.8-9.5) per 100,00 person-years.[19]
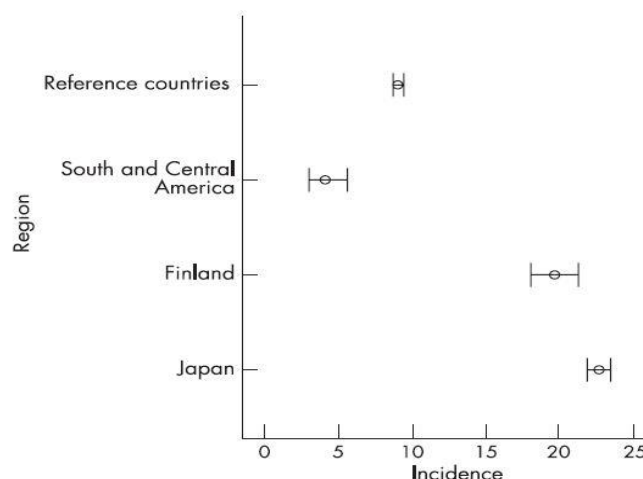
Figure 1-1 Incidence of SAH by region. Incidences per 100, 000 person-years, with corresponding 95% CI. All countries other than Japan (seven studies), Finland (six studies), and South and Central America (3 studies) were pooled in a reference group[19]

More recent systematic reviews support the previous results in terms of geographic variation in the incidence of aSAH. In a review based on the World Health Organization (WHO) regions with incidence studies conducted between years 1990-2016, the crude incidence of aSAH was estimated in these regions.[20] The studies were population and hospital-based with a prospective, retrospective or cross-sectional study designs included. The lowest incidence was recorded in the Eastern Mediterranean Region (EMR) 0.71 (95%CI 0.17-1.55) per 100,000 person-years and highest in the Western Pacific Region (WPR) 12.38 (95% CI 8.58-16.87) per 100,000 person-years (**Figure 1-2**). In the same study, the authors reported that the incidence in high-income countries was 8.30 (95% CI 6.72-10.03) per 100,000 person-years, which was higher compared to low and middle-income countries where the incidence was 2.56 (95% CI 1.51-3.86) per 100,000 person-years.[20] In an updated review that included studies from 1960 to 2017, the highest incidence of SAH was reported for Japan at 28.0 (95% CI 25.3-31.0) per 100,000 person-years followed by Finland with an incidence of 16.6 (95% CI 13.4-20.5) per 100,000 person-years. The lowest incidence of SAH was in Asian countries excluding Japan with an incidence of 3.7 (95% CI 0.1-13.3) per 100,000 person-years.[21] A recent update from the Global Burden Diseases (GBD) study from 1990-2017 also showed geographical variation in incidence rates of SAH. Confirming previous findings, the highest incidence rates were in Japan with 47 cases (95% UI 43-52) per 100,000 and lowest in China and Poland with 9 cases (95% UI 8-10) per 100,000.[30] A decline was noticed in different regions except Japan with a yearly increase of 1.6% since 1977.[21]
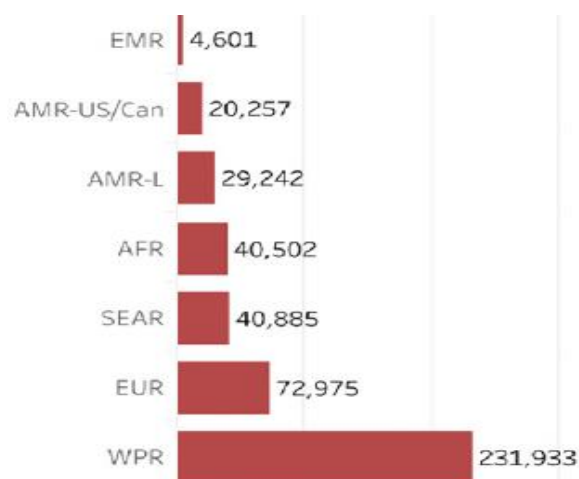
Figure 1-2 Estimated number of affected persons with aSAH per annum by WHO region; EMR, Eastern Mediterranean region; AMR-US/Can, United States/Canada; AMR-L, American region-Latin America; AFR, African region; SEAR, South-East Asia region; EUR, European region; WPR, Western Pacific region[20]

There are several proposed reasons for the regional differences in the incidence of aSAH. The incidence in Japan has been reported to be high in comparison to other countries. It is hypothesized that in the Japanese population there could be a contribution from genetic and environmental factors including different characteristics of aneurysms, but these have not been explored in detail.[31] In the Finnish population the greater incidence may be related to greater rates of familial SAH (e.g. clustering within families) compared to other western countries. This is explained by less immigration and the formation of small communities compared to other regions.[32] Authors of another study postulated that differences in connective tissue properties potentially associated with genetics (and/or environment) could cause a higher risk of aneurysm rupture in certain populations than others.[33] Identifying factors associated with a higher incidence in certain regions could be important in preventing or treating the causes that could lead to aSAH.

1.2.1.2 Incidence in Australia

The incidence of aSAH has been recorded in various regions of Australia across different periods. The recent GBD study reported the incidence of SAH in Australia in 2017 of 12.4 (95% CI 11.0-14.0) per 100,000 people per year.[30] We also observe different estimates of incidence in different regions of Australia (**Table 1-2**). The higher incidence in some places compared to others could be explained by better diagnostic procedures that influence detection rates. Regional differences in the underlying risk factors for aneurysm formation and rupture, such as smoking and hypertension, could also play a role.[34] These studies also have different designs ranging from retrospective hospital-based studies to prospective population-based studies, which may result in different estimates.

Table 1-2 Incidence of SAH in Australia

Location	Time-period	Incidence (95% CI) per 100, 000 person-years
Perth [35-37]	1989-1990	8.7 (5.5-13.7)
	1995-1996	3.0 (0.8-7.6)
	2000-2001	8.4 (4.8-14.7)
***Melbourne**[38, 39]	1996-1997	9.0 (5.1-15.8)
	1997-1999	9.1 (7.0-11.9)
****Adelaide, Hobart, Perth**[40]	1995-1998	8.1 (7.4-9.0)
Adelaide[41]	2009-2010	4.7 (2.3-9.9).
South Australia[42]	2009- 2011	2.6 (1.1-6.3)
Tasmania[43]	2010-2014	11.38 (9.93-12.83)

* Melbourne for North East Melbourne stroke study (NEMESIS)
** Australian cooperative research on subarachnoid haemorrhage study (ACROSS) also included cases from Auckland (New Zealand)

1.2.2 Sex differences in the incidence of aSAH

Various studies have reported sex differences in the incidence of aSAH, with higher estimates in women compared to men as summarized in **Table 1-3.**

1.2.3 Prevalence of unruptured intracranial aneurysm (UIA)

UIA can lead to a ruptured intracranial aneurysm, which is a catastrophic consequence. The UIA has mean prevalence of 2.8% (95% CI 2.0%-3.9%).[44] A higher prevalence has been observed in women than men with ratio of 3:2 with increase in prevalence with age.[45, 46] It is important to appreciate that greater incidence of aSAH in women is directly related to a higher prevalence of UIA in women than men. Female sex is a well-known risk factor for UIA.[44]

Table 1-3 Sex differences in the incidence of aSAH

Study	Study period	Study design	Incidence (95% CI) in men/100,000 person-years	Incidence (95% CI) in women/100,000 person-years
de Rooij et al[19] (2007)	1960-2005	Systematic review of prospective population based (overall)	9.2 (8.4-10.2)	11.5 (10.6-12.6)
Etminan et al[21] (2019)	1960-2017	Systematic review of prospective population based (overall)	9.3 (7.7-11.3)	11.5 (9.5-13.9)
Etminan et al[21] (2019)	1960-2017	Systematic review of prospective population based (Japan)	19.5 (14.2-26.8)	22.9 (15.7-33.5)
Etminan et al[21] (2019)	1960-2017	Systematic review of prospective population based (Europe)	10.7 (8.2-13.9)	12.5 (10.1-15.4)

Study	Study period	Study design	Incidence (95% CI) in men/100,000 person-years	Incidence (95% CI) in women/100,000 person-years
Etminan et al[21] (2019)	1960-2017	Systematic review of prospective population based (Asia)	14.8 (10.8-20.3)	17.8 (12.4-25.7)
Ziemba-Davis et al[47] (2014)	2005-2010	Prospective hospital-based (USA: in 12 central Indiana counties)	13.0*	30.2*
Nichols et al[43] (2018)	2010-2014	Retrospective population based (Australia)	6.91 (5.30-8.52)	15.73 (13.34-18.13)

*95% CI is not reported in the study

The age-adjusted incidence estimates were also higher in women compared to men.[21, 43] It is obvious that women suffer more from this rare, yet an often fatal type of stroke than men, in different time-periods and across countries.

1.3 Existing literature in determining sex differences in risk factors for aSAH

Examining studies that have reviewed the risk factors for aSAH could help answer the question of why aSAH is more common in women than men. Previously, two systematic reviews[48, 49] were conducted where the authors examined sex differences in the prevalence of risk factors and/or the effect of risk factors on the occurrence of SAH.

In one review, common risk factors including hypertension, smoking, and alcohol use were compared between men and women.[48] The estimates were pooled separately for longitudinal studies and case-control studies. These risk factors increased the risk of SAH in men and women equally. In the second review, the authors compared hypertension, smoking, alcohol intake, hypercholesterolemia, rigorous physical exercise, 'lean' body mass index (BMI) defined as BMI<22, non-white ethnicity and diabetes as risk factors for SAH between the sexes.[49] The authors reported similar findings regarding the lack of a sex difference in the risk of SAH associated with hypertension, smoking, and alcohol intake. Diabetes mellitus

decreased the incidence in women compared to men, while there was no difference by sex for likelihood of aSAH with rigorous physical exercise, 'lean' BMI, or non-white ethnicity.

These previous reviews also included studies of women-specific risk factors. One review showed that use of oral contraceptives (OCPs) and hormone replacement therapy (HRT) was not associated with the risk of SAH in women.[48] In the other review, the authors also did not find an association for the risk with OCPs but reported that the use of HRT tended to lower the risk of aSAH but this was without statistical significance.[49]

In these reviews, it is evident that a limited number of risk factors were examined. For example, a family history of aSAH or menstrual and hormonal factors in women were not included. There could be other risk factors that were not considered in these reviews and examining those factors might help in explaining the sex differences in the incidence of aSAH. These may include the anatomical location,[50-52] size[50, 51] and shape of aneurysm,[53] as these are known aneurysm-related risk factors for aSAH. There is a need for a detailed, updated systematic review on the sex differences in the effect of all possible reported risk factors for aSAH. This can help in identifying the causative factors that result in a higher incidence of the disease in women compared to men. In turn, this information could be used to inform sex-specific prevention strategies for aSAH.

The existing reviews were also not restricted to aneurysmal causes of SAH and examining the sex differences in risk factors was not the main objective of the authors with all examining risk factors between sexes as a sub-analysis. Restricting to aSAH could be important as this might strengthen evidence regarding what factors are specifically related to aneurysmal rupture. This may give new insights into the pathological mechanisms behind the disease.

The above-mentioned limitations in existing review studies suggest there is a need for a new systematic review specifically comparing risk factors for aSAH between men and women.

1.4   Outcomes of aSAH

Following an aSAH there are many potential outcomes measured in epidemiological and clinical studies. These include mortality or survival, functional outcome or 'disability', discharge destination and health-related quality of life (HRQOL).

Mortality is usually defined as the number of deaths in a specific population during a specified time period. Mortality rate is the number of deaths per 100,000 persons during a specified time

period. The data on mortality can be obtained from hospital records, death certificates, national data linkage of death registers.

Survival is the percentage of patients with a disease of interest who survived for a certain period, for example, 1 year or 5 years after the initial diagnosis. It is therefore used to measure prognosis of a disease.

Functional outcomes describe a person's ability to perform 'daily' tasks. They can be described using the International Classification of Functioning, Disability, and Health developed by the WHO.[54, 55] This document uses the blanket term 'disability' for 'impairments', 'activity limitations' or 'participation restrictions'. To describe the above-mentioned domains, various assessment tools have been devised. To measure functional outcome in stroke patients, the commonly used scales are the modified Rankin scale (mRS),[56] Barthel index (BI)[56] and Functional Independence Measure (FIM).[57] The data on functional activity is collected through face to face interviews, telephonic or video recorded interview or structured questionnaires.[58]

Health-related quality of life (HRQOL) is "an individual's or a group's perceived physical and mental health over time".[59] HRQOL is a multidimensional concept that includes domains associated with physical, mental, emotional, and social functioning.[60] There are different scales used to measure HRQOL. One commonly used instrument is EuroQOL five dimensions questionnaire (EQ-5D).[61] The self-assessment questionnaire includes a self-reported description of the subject's current health in 5 aspects including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The Short-Form 36 (SF-36) is another commonly used tool that is used to assess HRQOL.[62] This comprises of 36 questions for a self-reported assessment of the patient in 8 domains of health, including physical functioning, physical role, pain, general health, vitality, social function, emotional role, and mental health.[63]

Examining these outcomes after aSAH with consideration of sex could be helpful to add further evidence to literature and devise sex-specific interventions to improve outcomes if differences are observed.

1.5   Sex differences in outcomes of aSAH

Studies of outcomes after aSAH may focus on different time frames, typically defined as short term (e.g. 1 month) or long term (e.g. 1 year or more after the event).

The short-term outcomes after aSAH between the sexes have been discussed in a limited number of studies. Most studies report that the prevalence of unfavourable outcome was higher

in women, although many differences were non-significant.[64-68] The details of the studies are described below.

1.5.1 Survival

Existing studies have found similar in-hospital mortality between men and women after aSAH. In a Dutch prospective hospital-based study conducted from 1990 to 2010 which included 1,761 patients, the authors examined in-hospital mortality.[69] The risk ratio (RR) in women compared to men for in-hospital mortality was 0.94 (95% CI 0.82-1.07). In a Swiss prospective hospital-based study with 1,866 cases from 2009 to 2015, the authors measured death during hospital stay which showed a higher proportion of in-hospital death in women (64%) than men (36%).[67] In a retrospective hospital-based study in Switzerland conducted on 120 patients with aSAH admitted between 2009 to 2011, the authors reported no statistically significant difference by sex in ICU mortality (men 5% vs women 12%, p=0.34) and in-hospital mortality (men 16% vs women 23%, p=0.47).[65]

Previous studies of survival at 28 days or 1 month after aSAH have also generally not found a difference between men and women. In a Dutch nationwide prospective hospital-based study on 9,403 patients of SAH conducted between 1997 and 2006, the authors observed that 1-month crude risk of mortality for SAH for women was 35.3% (95% CI 34.1-36.6%) and in men, it was 31.7% (95% CI 30.1-33.3%).[66] They also stated that over the years they noted a decrease in the risk of death in men but not women. This was attributed to severity, the timing of treatment and medical complications following treatment. In a Swedish prospective hospital-based study between 1987 and 2002 investigators identified 18,443 SAH episodes.[68] Case fatality rate at 28 days was higher in women (32.5%) than in men (30.5%). The relative risk (RR) adjusted for age, sex, region was RR 1.06 (95% CI 1.02 to 1.11). A retrospective population-based study which was conducted in the UK from the year 1992 to 1996, 800 patients experiencing first-ever SAH were identified.[70] The authors reported that the relative risk of death was slightly greater in women at 24 hours (RR 1.25 95% CI 0.85–1.84), at 7 days (RR 1.23 95% CI 0.89–1.69) and at 1 month (RR 1.15 95% CI 0.84–1.57) after SAH when adjusted for age, without statistical significance. In a retrospective hospital-based study from Martinique between 2007 and 2013, authors included 121 cases of SAH.[71] The authors found more men (34%) died compared to women (20%) within 1 month of SAH. In a retrospective hospital-based Scottish study conducted between 1986 and 2005, the authors noticed that 1-month case fatality increased with age in both men and women.[72] At age <40 years, the case

fatality at 1 month was 29% in men and 25% in women and increased to 60% in men and 57% in women who were 70 years or older.

Existing studies of survival up to 3 months after aSAH have generally not identified any sex differences. In a Dutch prospective hospital-based study, the risk of case fatality at 3 months was somewhat lower in women RR 0.93 (95% CI 0.82-1.06) compared to men when adjusted for age, condition on admission and aneurysm site.[69] The outcome was, therefore, better in women than men, but this was not statistically significant. In another retrospective hospital-based study on 617 patients with aSAH from 2005 to 2010 in the UK, authors observed outcome at 3 months.[52] The death rate was similar between men (19%) and women (20%). In a multicentre randomised control trial study on a high dose of nicardipine in North America, the authors followed up patients for 3 months.[64] They did not detect any difference by sex in mortality after aSAH where the death rate in women was 19% compared to 17% in men.

Of note, the above-mentioned studies were not designed exclusively to examine sex differences in mortality after aSAH and a majority of these did not specifically examine aSAH. The limitations of these studies are highlighted at the end of this section.

1.5.2 Functional outcomes

A smaller number of studies have examined sex differences in functional outcomes after aSAH. Findings of some of these studies are described here. In a retrospective hospital-based cohort study in the UK mentioned previously,[52] poor functional outcome was measured using mRS (4-6). The odds ratio (OR) of poor outcome in women compared to men was OR 0.89 (95% CI 0.61-1.32, p=0.57) in univariable and OR 0.71 (95% CI 0.45-1.11, p=0.13) in multivariable analysis, adjusted for age, aneurysm size and location and stroke severity. Therefore, no statistically significant difference was noted between the sexes. In a Swiss retrospective hospital-based study, described previously,[65] the investigators noticed that the odds of poor functional outcome (mRS 4-6) was OR 1.19 (95% CI 0.44-3.19) for women compared to men when adjusted for age and severity score. The authors did not report univariate results.

Very few studies have examined sex differences in functional outcomes after aSAH. Further research is required to explore this area in aSAH. A summary of gaps in the evidence regarding outcomes of aSAH is described below.

1.5.3 Summary of findings and evidence gaps

It is noted that the majority of the studies showed that there was no difference by sex in the outcomes after SAH or aSAH, specifically. But most of the studies discussed here had certain limitations meaning that it is not conclusive whether there are sex differences in outcome after aSAH. First, there are few studies designed to examine sex differences in the outcomes after aSAH.[52, 64-66, 69] As such, in most studies sex differences were compared in an unadjusted analysis without further analysis of factors contributing to poor outcome in men and women. Second, the existing studies of outcome after aSAH examining sex differences were mostly conducted at a single-centre and were hospital-based, with the exception of one nation-wide study on aSAH[66] and one multicentre trial of a drug.[64] A multicentre study is likely to have more generalisable findings compared to a single-centre study. Multicentre studies could help increase the power of a study of rare diseases like aSAH that have lower case volume. Third, some of the studies were not specific to the aneurysmal origin of SAH.[68, 70, 72] Fourth, excluding the population-based and a few hospital-based studies,[66, 68, 70] most of the studies had a small sample size. Therefore, there is a need for adequately powered, multicentre studies exclusively examining aSAH patients designed to examine sex differences. These studies should analyse the comprehensive list of factors that might explain these differences. Also, these studies will be useful because this could help in identifying the factors that predict sex differences in outcomes and planning sex-specific management leading to timely prevention or intervention of the identified factors, therefore, improving survival.

1.5.4 Long term outcome

There are few studies that have examined sex differences in longer-term outcomes after aSAH with some inconsistencies in findings regarding sex differences. This literature is summarised in the following section.

1.5.4.1 Outcome at 1 year

A small number of investigators have examined sex differences in survival, functional outcomes and HRQOL at 1 year after SAH or aSAH. Most of these studies were hospital-based and did not exclusively examine aSAH.[73, 74] These were limited to a certain group of patients (e.g. only patients with a better clinical grading score [75]), carried out at one institution,[76] or had high loss to follow up.[77, 78] The findings of these studies are discussed below.

Among studies of survival after aSAH, most have not found a difference between men and women. In one study based on Medicare beneficiaries from 1994 to 1996 who were admitted for stroke in the hospitals of the states of Indiana and Kentucky in the USA, authors examined long term mortality.[73] For SAH, they observed that the mortality rate at 1 year was slightly higher in men (59%) compared to women (52%). The rate ratio for all-cause mortality at 1 year in men compared to women was 1.13 (95% CI 0.99-1.30) when adjusted for age, therefore no sex difference was detected. Similar findings were reported by authors for a cohort study in the Netherlands with data on different types of strokes for the patients admitted in 1997 or in year 2000.[74] The authors compared mortality at multiple time points between the sexes among 1,884 patients with SAH. The 1-year mortality rate in women was 40% and in men was 39%. The risk of mortality in women when standardised for age at 1 year was 0.91 (95% CI 0.80-1.04). The 1-year crude and age-adjusted hazard ratios (HR) for case fatality in women compared to men (HR_{crude} 1.03 95% CI 0.88-1.19, $HR_{adjusted}$ 0.99 95% CI 0.85-1.15) were not different.

The International Subarachnoid Aneurysm Trial (ISAT) was a prospective randomised controlled trial conducted at multi-centres that compared the results of coiling and clipping.[75] There were 2,004 patients in the study followed up into the longer term. The authors' calculated standardised mortality ratio (SMR) in men and women conditional on survival at 1 year. The results were not different between women (SMR 1.65 95% CI 1.32-1.98) and men (SMR 1.46 (95% CI 1.09-1.83). In a Finnish study, 1,537 patients with aSAH between 1977 and 1998 were followed up for 7.5 years.[76] The SMR in patients who had good recovery at 1 year was lower in men (SMR 1.84 95% CI 1.36-2.48) than women (SMR 2.13 95% CI 1.72-2.65). Except for age, many studies did not explore other factors that might be associated with the sex and outcome including aneurysm characteristics, complications and severity of stroke. Studies accounting for these design issues should be conducted to examine sex differences in 1-year mortality.

Some authors have also examined sex differences in functional outcomes at 1 year after aSAH. A study was conducted in Germany with 203 aSAH cases between 2012 and 2017 to observe the effects of different co-morbidities and risk factors on the outcome at 1 year after aSAH.[79] They compared poor outcome (mRS 3-6) compared to the good outcome (mRS 1-2). The odds of poor outcome (OR 0.64 95% CI 0.23-1.75, p=0.38) and death (OR 0.89 95% CI 0.35-2.27, p=0.80) at 1 year was not significantly different in women compared to men. Another multicentre prospective study in China included 324 poor-grade aSAH patients cases from 2010 to 2012.[80] The outcome was based on mRS with scores >4 defined as a poor outcome.

Poor outcome was more common in women (56%) than in men (44%). The odds for poor outcome in women in the unadjusted analysis was OR 1.7 (95% CI 1.1-2.6, p=0.02). The authors did not mention sex in their multivariate analysis. An important limitation is that these studies did not examine role of sex as their main aim. Also, these studies were either limited to certain category of patients[80] or were single-centred,[79] meaning the results might not be generalisable. More research is therefore warranted to examine sex differences in functional outcome at 1 year after aSAH.

Very few studies explored sex differences in HRQOL at 1 year after aSAH. In a Swedish hospital-based study on 755 patients admitted between 1996 to 2010, authors examined EQ-5D at a median follow-up time of 1 year.[81] Female sex predicted worse HRQOL regarding domains of pain/discomfort and anxiety/depression compared to men. Authors of a Norwegian study with a cohort of 60 patients between January 2001 to July 2001 examined HRQOL at 1 year.[77] They used World Health Organization Quality of Life Instruments (WHOQOL-BREF) covering four domains of life including physical, mental, social, and environmental. This questionnaire was completed by 40 participants. The authors observed that women were significantly less satisfied with the ability to perform daily tasks and had more negative emotions, such as being sad, anxious or depressed, than men. In a study with 601 cases of SAH between 1998-2008 in Germany, HRQOL was assessed using SF-36.[78] Only 253 patients responded to the questionnaire, therefore, there was missing data regarding outcome of all the patients included in the study. The authors did not find a difference in HRQOL between men and women. The follow-up time was not mentioned in this study.

There appears some evidence of sex differences in HRQOL after SAH/aSAH. However, the above-mentioned studies did not aim to examine sex difference in HRQOL meaning their analyses might not have been designed appropriately to answer this research question. Further, the studies were single-centred and with a large number of patients lost to follow up, which might affect the generalisability of findings. More studies focussing on sex difference in HRQOL after aSAH need to be conducted to understand patient-centred outcomes and the role of factors contributing to these differences. This could assist with the development of sex-specific measures to improve HRQOL after aSAH.

1.5.4.2 Outcome at or after 5 years

There have been few studies that have reported sex differences in outcomes at >5 years after the aSAH. These studies are mostly hospital-based cohorts with cases followed over time. In

general, these studies have found no difference by sex in mortality,[74] SMR,[82] RER of mortality[83] and proportion of patients[84] deceased at 5 years or beyond. The results of these studies are summarised below.

Authors of a cohort study in the Netherlands with 1,884 cases of SAH between 1997-2000 found that the 5-year mortality rate was 44% in women and 42% in men.[74] The crude and age-adjusted HR for case fatality in women compared to men at 5 years (HR_{crude} 1.04 95% CI 0.91-1.21, $HR_{adjusted}$ 0.99 95% C 0.86-1.15) were not different.

Authors of a study based on 752 prospectively collected cases of SAH in the Netherlands, calculated standardised mortality ratio with a mean follow-up time of 8.1 years.[82] The SMR observed in women 2.0 (95% CI 1.6 to 2.6) was higher than men 1.3 (95% CI 0.9 to 1.8). In a Finnish study comparing sporadic and familial aneurysms, authors calculated long term excess mortality in 1,746 patients who were survivors 1 year after aSAH.[83] The median time of follow-up was 12 years. The RER of mortality in 1-year male survivors of aSAH was 1.63 (95% CI 0.98-2.71). A retrospective study conducted in Finland followed patients with aSAH who were alive 1 year after the onset.[84] There were 3,078 patients alive after 1 year who were treated between 1980 and 2007. According to the authors of the study, sex did not influence long term excess mortality. The excess mortality at 20 years was 18% for women and 17% for men; whereas, at 30 years, it was 32% in both sexes.

Overall, few differences have been observed in outcomes between men and women in the longer-term. It is important to highlight that none of these studies were designed to examine differences in long term outcomes after aSAH by sex. This may affect the ability to draw conclusions as the analyses were not designed to answer this research question. Most of the above-described studies were conducted at a single-centre making generalisability of results questionable. Most of the authors of these studies did not mention important potential covariates including vascular risk factors, aneurysm features or complications. Loss to follow up was high in some studies potentially compromising the validity of results. There is a need for studies specifically designed to examine sex differences in survival, functional and quality of life measures. Larger studies across multiple centres would be preferable as these may be more representative of a wider range of aSAH patients.

1.6 Factors that might explain sex differences in outcome after aSAH

1.6.1 Risk factors

Differences in the risk factors associated with aSAH between men and women may explain differences in outcomes, if they are found to exist.

1.6.1.1 Age

Greater age is a non-modifiable risk factor for worse outcomes after aSAH. Although the majority of aSAH patients are in younger age groups compared to ischaemic stroke, increasing age within this population group is associated with a risk of poor outcome of aSAH as confirmed in several studies.[80, 85, 86,87] In cohorts of aSAH, women are relatively older than men.[88] Very few studies have explored the contribution of age in sex differences in outcomes and the reported outcome was not different between men and women when age was taken into account.[52, 69]

1.6.1.2 Vascular risk factors

The presence of vascular risk factors differs by sex and also predicts the outcome in aSAH patients. A history of hypertension was associated with a higher risk of long-term mortality, as reported by some authors.[85, 89] Premorbid hypertension is associated with more severe SAH with a large amount of bleeding in cisterns and intraventricular spaces predicting poor prognosis after aSAH.[90] There is an increase in the risk of severe complications including delayed cerebral ischaemia (DCI)[91] and cerebral infarction,[92] leading to higher mortality after aSAH.[93] Sex differences in hypertension in people with aSAH[94, 95] have been reported previously. If and how this contributes to outcome after aSAH in men and women is unknown and needs further investigation. Smoking could lead to symptomatic vasospasm or DCI after the event.[96-98] Some studies showed better outcomes in smokers [79, 99] but a recent study explained this paradox was owing to early deaths in patients with a smoking history or perhaps poorer risk factor profile resulting in worse outcomes of aSAH.[100] Sex differences exist in smoking prevalence, with this more common in men than women.[95] Whether smoking contributes to sex differences in outcomes after aSAH remains unknown. Alcohol consumption is also associated with worse outcomes after aSAH. It can lead to hypertension and the occurrence of DCI.[101] There are known sex differences in intake of alcohol[94] but how these explain sex differences in the outcome needs to be examined.

There are known sex differences in the common risk factors for aSAH, but if and how these risk factors contribute to outcomes after aSAH needs further investigation. If particular risk factors are found to contribute to differences in outcomes between men and women, this information may be useful for devising sex-specific strategies for prevention of aSAH, reduced complications and better outcomes.

1.6.2 Aneurysm characteristics

Characteristics of the aneurysm that ruptures in aSAH are associated with survival and functional outcome after aSAH, with some known sex differences.

Aneurysm formation can take place around the circle of Willis. There are some studies which studied the association of poor outcome with the site of rupture. In a study with 3,498 aSAH patients, authors examined various pre-operative factors which were associated with poor Glasgow outcome scale (GOS).[85] An unfavourable outcome was defined as being deceased or severely disabled. Posterior circulation aneurysms were associated with poor outcome HR 1.53 (95% CI 1.14-2.04). Some authors suggest that a poorer outcome is associated with aneurysms in the anterior circulation,[102] while some suggested no influence of the aneurysm location on the outcome.[103] Sex differences were also observed in the location of a ruptured aneurysm in different studies. In a study of 608 aSAH patients between 2002 and 2011, authors observed that the most frequent site for the ruptured aneurysms in women was at the internal carotid artery (42%) while in men common locations were the anterior cerebral and anterior communicating artery (47%).[50] In a clinical trial of nicardipine, 906 patients were enrolled and internal carotid artery was common in women (36%) as the site of rupture while anterior cerebral and anterior communicating artery in men (46%).[64] Similarly, authors of another study reported a higher prevalence of aneurysm at internal carotid artery, prevalence ratio (PR) 1.71 (95% CI 1.38-2.13) and middle cerebral artery PR 1.14 (95% CI 0.92-1.41) in women compared to anterior cerebral and posterior circulation.[69] A case series of 617 aSAH cases also showed similar results.[52] The most common location of the ruptured aneurysm in women was internal carotid artery (women 40% vs men 18%) and anterior cerebral-anterior communicating artery in men (women 26% vs men 45%). A retrospective study on 2,835 patients of aSAH also reported similar results in men and women.[51]

Aneurysm size was also found to be a predictor of unfavourable outcome after aSAH.[104, 105] Some studies investigated sex differences in the size of a ruptured aneurysm. However, the authors of these studies did not detect any difference by sex in the size of the ruptured

aneurysm.[52, 64] These studies did not examine the role of aneurysm characteristics including consideration of sex and outcomes.[64] It could be postulated that the high amount of early mortality in aSAH than other stroke types could also be due to posterior location of the ruptured aneurysm, which results in neurological damage associated with a high risk of death (e.g. respiratory control).[106]

Except for a few studies,[52, 69] the main aims of most of these studies was not to examine sex differences in aneurysm characteristics or observe their association with outcome. Most of the studies examining the effect of sex described only one aneurysm characteristic, for example, the site of rupture. We need more evidence regarding sex differences in the aneurysm characteristics (site, size, location in circulation) and how these differences describe the outcome. If aneurysm characteristics are found to contribute to differences in outcomes between men and women, this information may be useful for predicting outcomes. It may also lead to advances in understanding the pathophysiology of aneurysm rupture.

1.6.3 Neurological complications

Neurological complications after aSAH are associated with poor outcomes.[52, 85, 89] Sex differences have been observed in some neurological complications after aSAH. The most known complications are hydrocephalus, rebleeding, delayed cerebral ischaemia (DCI), cerebral infarction, seizures, and neurological infections.

Of all complications, it has been observed that women are more likely to suffer from DCI compared to men.[88, 107] There has been a use of different terminologies for DCI. These include 'delayed neurological deficit', 'symptomatic vasospasm', 'vasospasm' or sometimes 'cerebral infarction'. It is defined according to National Institute of Neurological Disorders (NINDS) as "the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies." [24, 108] A systematic review conducted for studies published until 2012 identified various predictors of DCI.[98] The authors observed limited evidence of sex being a predictor for DCI with the pooled odds for women compared to men being OR 1.2 (95% CI 0.8-1.8). In 2018, a study observed sex difference in DCI and cerebral infarction using Subarachnoid Haemorrhage International Trialists (SAHIT) repository.[88] This

included 6,713 patients with more women than men. The authors found that female sex was a predictor of DCI (OR 1.38 95% CI 1.09-1.74, p=0.007). Authors of another case series also reported that sex differences are present in clinical deterioration (OR 2.8 95% CI 1.3-6.0) and cerebral infarction (OR 2.4 95% CI 1.0-5.5) when adjusted for age, hypertension, severity scores and aneurysm location.[107]

Cerebral infarction after SAH or aSAH is defined as "the presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from a ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI." [24, 108] In the study previously mentioned based on identifying independent predictors of cerebral infarction, the authors did not detect any significant association of cerebral infarction with sex (OR 1.02 95% CI 0.81-1.30, p=0.84).[88]

Therefore, some studies show that sex is a predictor of DCI but how these sex differences might play a role in the outcome after aSAH is not clearly explained. Further exploration to identify the role of sex in DCI and its contribution in outcome after aSAH is warranted.

Hydrocephalus is increased intracranial pressure because of lesser absorption of cerebrospinal fluid (CSF) due to accumulation of blood after SAH. It is a common complication, with one study based on 897 patients with aSAH showing the development of hydrocephalus in 26% of the patients.[109] The authors found a statistically significant association of female sex with the development of hydrocephalus. In another study conducted on 718 patients with aSAH, 152 developed shunt-dependent hydrocephalus that is they required ventriculoperitoneal shunt to treat hydrocephalus.[110] The authors noted that female sex was associated with hydrocephalus in addition to other factors including increasing age, more severe aSAH, posterior location of the ruptured aneurysm, intraventricular haemorrhage and clinical vasospasm. The reasons why women develop hydrocephalus more often than men and if this impacts outcome after aSAH has had limited exploration. There is therefore a need to further investigate the role of sex in hydrocephalus and how this might affect the outcome. This may help in developing management policies including improving diagnosis, identification of high-risk patients and timely intervention to reduce the risk of disability and death.

Rebleeding is the re-rupture of intracranial aneurysm. A meta-analysis of 7 studies published between 2000 and 2013 was conducted to determine the predictors of risk factors for rebleeding. [111] The authors found that men had more risk of rebleed compared to women with OR 1.46 (95% CI 1.11-1.92). Whether this high risk of re-bleeding in men compared to women contributed to differences in outcome has not been examined.

We observed that sex differences have been noted in some of the important complications of aSAH. It is unknown if and how these differences by sex in neurological complications contribute to differences in the outcomes between both sexes. If complications are found to contribute to differences in outcome between men and women, it might help in developing interventions to reduce complications or improve their management.

1.6.4 Severity

To predict the prognosis of aSAH many clinical and radiological scores have been devised. Most commonly used are the World Federation of Neurosurgical Societies (WFNS) score, Hunt and Hess scale, Glasgow Outcome Scale (GOS)[112] and modified Fisher grade.[113] WFNS uses the Glasgow coma scale (GCS) and the presence of focal neurological deficits to grade the severity of the disease with grading from I to V explained in

Table 1-4. Higher grades denote poorer prognosis.[114]

Table 1-4 World Federation of Neurosurgical Societies (WFNS) score

WFNS	GCS score	Motor deficits
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Modified Fisher score is a CT rating scale based on the thickness of cisternal subarachnoid blood and absence or presence of intraventricular haemorrhage (IVH) to predict symptomatic vasospasm [115] explained in **Table 1-5**.

Table 1-5 Modified Fisher scale

Modified fisher grade	Cisternal clot thickness	IVH
0	No	No
1	Focal or diffuse thin (<1mm)	No
2	Focal or diffuse thin (<1mm)	Yes
3	Thick (>1mm)	No
4	Thick (>1mm)	Yes

These severity scores are associated directly with poorer outcomes, including complications. The modified Fisher score predicts symptomatic vasospasm in SAH patients.[115] Poor grade patients indicated by worse Fisher or WFNS scores are more prone to complications of aSAH like rebleeding, hydrocephalus and DCI[116] or developing systemic complications.[117] It has been observed that more than 60% of the 'poor grade' patients with SAH die or become functionally dependent.[118] Therefore, in people with a poor grade SAH there is a higher chance of death or severe disability.

Sex differences in the severity of aSAH have been reported in a few studies. Authors compared severity scores including WFNS and Fisher score between men and women but did not find any difference.[52, 65, 69] The severity of the aSAH predicts complications, some of which demonstrate sex differences. However, it is currently unclear if there is a difference by sex in the severity of aSAH. The role that severity of the aSAH might play in sex differences in outcomes requires investigation in a high-quality multicentre study.

1.6.5   Management

Clinical guidelines for the diagnosis and treatment of aSAH provide a protocol for management associated with better outcomes.[119, 120] Evidence-based processes of care utilization could be predictors of outcomes of aSAH. According to European and American guidelines recommendations include: imaging with a non-contrast head computed tomography (CT)[121] scan for the diagnoses of aSAH, aneurysm detection computed tomography angiography (CTA) and/or digital subtraction angiography (DSA); use of antihypertensives in the emergency department (ED) to reduce blood pressure with a cut off level of systolic blood pressure (SBP)>160 or 180mmHg; administration of medication including nimodipine[122, 123] to prevent DCI and improve the outcome[5]; treatment of aneurysm by clipping or coiling[124] and reduction of raised intracranial pressure through the extra-ventricular drain (EVD) or ventriculoperitoneal shunt placement (VPS). We know of studies based on ischaemic stroke

that have observed sex differences in receipt of evidence-based processes of care[125, 126] but to the best of our knowledge, no study has examined sex differences in adherence to treatment guidelines for aSAH.[127]

1.7   Summary

There is still research required to develop more evidence to explain the difference in the incidence of aSAH by sex. Possible reasons for a higher incidence of aSAH in women than men include changes in the reproductive hormonal levels with age, differences in the prevalence or effect of common risk factors like smoking on aneurysm formation or rupture or potentially genetic factors. Regarding the outcomes of aSAH, there is some evidence that poorer outcomes are slightly more common in women than men, albeit non-significantly. The potential factors and covariates associated with poor outcome in various studies include age, risk factors like hypertension, smoking status, neurological complications, aneurysm characteristics, and severity of aSAH. Evidence-based processes of care for aSAH and their relationship with outcome after aSAH has not been investigated to date. The current literature suggests a need for more research based on sex differences in aSAH taking into consideration all above-mentioned factors. These types of studies could increase our understanding of aSAH including how to improve management and outcomes.

Aims

The aims of the thesis are to:

1) Identify sex differences in the risk factors for aSAH
2) Examine sex differences in the short and long-term outcomes of aSAH
3) Identify factors contributing to poor outcome in women compared to men

Research Questions

1. What are the sex differences in the risk factors for aSAH in the existing literature and do they explain the greater incidence in women?
2. Are there sex differences in discharge destination, mortality and poor functional outcomes in the short and long-term after aSAH?
3. Are there sex differences in the receipt of evidence-based care after aSAH?
4. What is the contribution of factors including pre-event factors like age, hypertension and smoking status or clinical factors like complications, aneurysm characteristics or care in the sex differences in short and long-term outcomes after aSAH?

Thesis organization and guide to chapters

This thesis uses a systematic review and original analyses using two datasets (REDucing Delays In aneurysmal Subarachnoid Haemorrhage study [REDDISH] and INternational STRoke oUtComes sTudy [INSTRUCT] to address the above-mentioned aims and research questions.

Chapter 1: Introduction

In this chapter, I describe the topics which I further discuss in my thesis. I have mentioned what is known in the literature regarding sex differences in the risk factors and outcomes, the gaps in knowledge and factors which could be contributing to sex differences in the outcomes.

Chapter 2: Methods and summary of participants from the REDucing Delays In aneurysmal Subarachnoid Haemorrhage (REDDISH) study

In this chapter, I explain the methods used to gather data for this study that forms the data source for chapters 3 and 4.

Chapter 3: Sex differences in risk factors for Aneurysmal Subarachnoid Haemorrhage: Systematic Review and Meta-analysis

I explain differences of risk factors in men and women in the form of narrative systematic review and meta-analysis. I compare risk factors for aSAH in both sexes to attempt to better understand the greater incidence of aSAH in women compared to men.

Published in Journal of the Neurological Sciences (2019).

Chapter 4: Sex Differences in Aneurysmal Subarachnoid Haemorrhage (aSAH): Aneurysm characteristics, Neurological complications, and Outcome

In this chapter, I examine the sex difference in discharge destination after hospital admission taking account of aneurysm characteristics and neurological complications.

Published in Acta Neurochirurchiga (2020).

Chapter 5: Adherence to evidence-based processes of care reduces one-year mortality after Aneurysmal Subarachnoid haemorrhage (aSAH)

This chapter focuses on sex differences in the provision of evidence-based processes of care for aSAH and how they affect 1-year survival.

Chapter 6: Sex differences in short and long-term mortality and functional outcome after subarachnoid haemorrhage (SAH) in INternational STRoke oUtComes sTudy (INSTRUCT)- A pooled analysis of the individual participant data

In this study, I explore differences between men and women in short and long-term mortality and functional outcomes after the event of aSAH and what factors contribute to sex differences.

Chapter 7: Discussion

In this chapter, I summarize the findings of the thesis and recommendations for future work in the field of aSAH.

Chapter 2: Methods and summary of participants from the REDucing Delays In aneurysmal Subarachnoid Haemorrhage (REDDISH) study

2.1 Background

Two of the results chapters in this thesis use data from the REDDISH study, which was a study designed to examine time to treatment and its association with outcomes after aSAH. See **Appendix E** for details on REDDISH study database. This thesis includes some secondary analysis of data from that study focusing on sex differences in clinical aspects and outcomes of aSAH. This chapter describes the methods of the REDDISH study in detail, including my role in data collection. It presents preliminary results relating to the characteristics of participants with a focus on sex differences. The final results chapter of the thesis uses data from a different study, an individual participant data analysis from stroke incidence studies with data on SAH. The methods for that study are contained within that study chapter.

2.2 Methods

2.2.1 Role in data collection

In the REDDISH study, I played a significant role in the data collection for the Tasmanian cohort of aSAH from 2010-2016. I extracted data for the confirmed and probable cases of aSAH. Probable cases were defined as suspected aSAH cases with definitive testing not available. After the potential cases were identified, I examined patient records including hospital discharge certificate, imaging details, medical records, and surgery details to confirm the cause for SAH. Because of medical background and training as an anatomist, I was well informed of the anatomy and physiology of the brain and used my knowledge and skill to identify the patients and search associated material to confirm case as an aSAH. After confirmation or probability of the cause as aneurysmal rupture, I extracted the information for the variables described later in the methods. For the Tasmanian population, data were collected in two phases. In the first phase, for cases between 2015-2016, I identified the confirmed and probable cases of aSAH. The data on excluded cases from the list of potential cases were also extracted with a reason for exclusion. The information for included cases was extracted in detail in the database. In the second phase, I extracted the data for already identified confirmed and probable cases of aSAH between 2010-2014.

2.2.2 Setting

This was a retrospective cohort study of all patients with aSAH across two tertiary referral hospital networks (Tasmania, population ~500,000 and South East Victoria, population ~1.2 million) in Australia from 1st January 2010 to 31st December 2016. Both hospitals are comprehensive cerebrovascular centres, receiving patients who experience aSAH from a network of urban, regional and rural hospitals. This study was approved by the Human Research Ethics Committee in Victoria (RES-18-0000-036A) and Tasmania (H0014563).

2.2.3 Identification of potential cases

Potential cases were identified using multiple overlapping sources including admission, discharge and ward lists for the emergency, neurosurgical and radiology departments across the tertiary centres and referring hospitals. A combination of International Classification of Diseases 10 codes (160.0-160.9, 167.1 and 169.0), as either a primary or secondary diagnosis, and keyword searches were used to ascertain potential cases. A standardised extraction form using data from radiology, pathology, and surgical reports, as well as the medical record, were used to confirm first ever aSAH. Potential cases were coded by one researcher in each site, and a neurosurgeon and/or an interventional neuroradiologist confirmed the diagnoses and resolved any discrepancies. Following a detailed review of medical records, patients with unruptured aneurysms were excluded, and only those with confirmed SAH were included in the final sample. The presence of subarachnoid haemorrhage was confirmed on either non-contrast CT-Brain or xanthochromia on lumbar puncture. CT-angiography (CTA), digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) were then used to find a cause, including an aneurysm, and characterise it. We excluded cases with a previous history of aSAH and other causes of subarachnoid haemorrhage including arteriovenous malformations (AVMs), trauma, amyloid angiopathy and non-aneurysmal SAH. The latter was only excluded where, despite multiple series of imaging tests, a cerebral aneurysm could not be demonstrated. After verifying the aneurysmal cause of SAH, information was extracted from the medical record and captured in REDCap.

2.2.4 Participants

Patients with confirmed or probable aSAH were part of the study who were admitted to the two hospital networks between 2010-2016. For Tasmania, there was an existing dataset for SAH participants between 2010-2014. The data for these patients were further extracted for the

confirmed and probable cases to match the new data extracted for people between 2015 and 2016.

2.2.5 Measures

The variables in the study included patient information (age, marital status, insurance, residence), medical history of patient (family history, pre-morbid conditions like coronary arterial disease, polycystic kidney disease, hypercholesterolemia, use of anticoagulants, behavioral factors like smoking status and alcohol intake), Charlson co-morbidity index (includes important risk factors like diabetes mellitus, liver disease, cancer, previous history of stroke or TIA, peptic ulcer disease), date and time of aSAH, symptoms of disease (headache, neck rigidity, vomiting, loss of consciousness and others), use of ambulance services (time of call, arrival at scene and hospital, management, triage), patients vital sign recorded in ambulance (pulse, systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, Glasgow coma scale (GCS), and hospital admission record (history, triage, time and date of arrival, information on vital signs and GCS, medications in emergency department, transfer to other hospital).

The data after hospital admission was extracted for severity scores which were the World Federation of Neurological Surgeons score (WFNS, I-V) and modified Fisher's score (0-4) from the CT scan. Imaging details were collected (date and time of CT/CTA/DSA/MRA) including aneurysm characteristics (side, size, location in circulation and site) and details on treatment (ventriculostomy, clipping/coiling, use of nimodipine, use of antihypertensives).

Data were extracted regarding complications including delayed cerebral ischaemia (DCI), cerebral infarction, hydrocephalus, rebleed, infections and other non-neurological complications. We also extracted information on the management of complications including endovascular therapy for DCI and information on active comfort measures. The definitions of neurological complications were standardised according to National Institute of Neurological Disorders and Stroke definitions (NINDS).[108] Clinical deterioration due to DCI was determined by the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes using clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies. The diagnosis of delayed cerebral injury was confirmed

according to NINDS definition as the presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MRI. Rebleeding was the occurrence of the bleeding from the aneurysm before and after treatment.[128] Hydrocephalus was the build-up of cerebrospinal fluid (CSF) due to obstruction in the flow within the ventricular system or impaired CSF reabsorption increasing intracranial pressure (>20mmHg)[129] and leading to permanent brain damage or death.[128]

2.2.6 Outcomes

Information was recorded for discharge destination (home, rehabilitation, transfer to other hospital or death) and Functional Independence Measure (FIM) score at the start of and discharge from rehabilitation. The REDDISH data was also linked to the National Death Index (NDI) for information on 1-year survival including causes of death.

2.3 Results

2.3.1 Participants

There were 1,957 potential cases of aSAH in the REDDISH study from South-east Victoria and Tasmania. After exclusion of non-aSAH cases based on inclusion criteria, the cohort comprised of 575 confirmed and 55 probable cases of aSAH. The breakdown of cases across two hospital networks and time-periods is described as follows.

In Tasmania, there were 304 potential cases from the year 2015-2016 out of which 64 confirmed cases and 1 probable case were identified. Detailed data extraction was performed for 208 variables. There were also data on cases of aSAH previously collected as part of a pilot study for cases between 2010-2014. For these cases, there was information missing on some variables included in the REDDISH study. For further information on these patients, I extracted data regarding 148 new variables for 159 confirmed and 26 probable cases. The data were also collected by trained researchers for the cases of SAH for South-east Victoria. There was a total of 1,363 potential cases from 2010-2016, and 354 were the confirmed and 28 probable aSAH cases. The two data sets were combined for this study.

Flow chart (**Figure 2-1**) below explains the selection of participants in REDDISH from the two hospital networks.
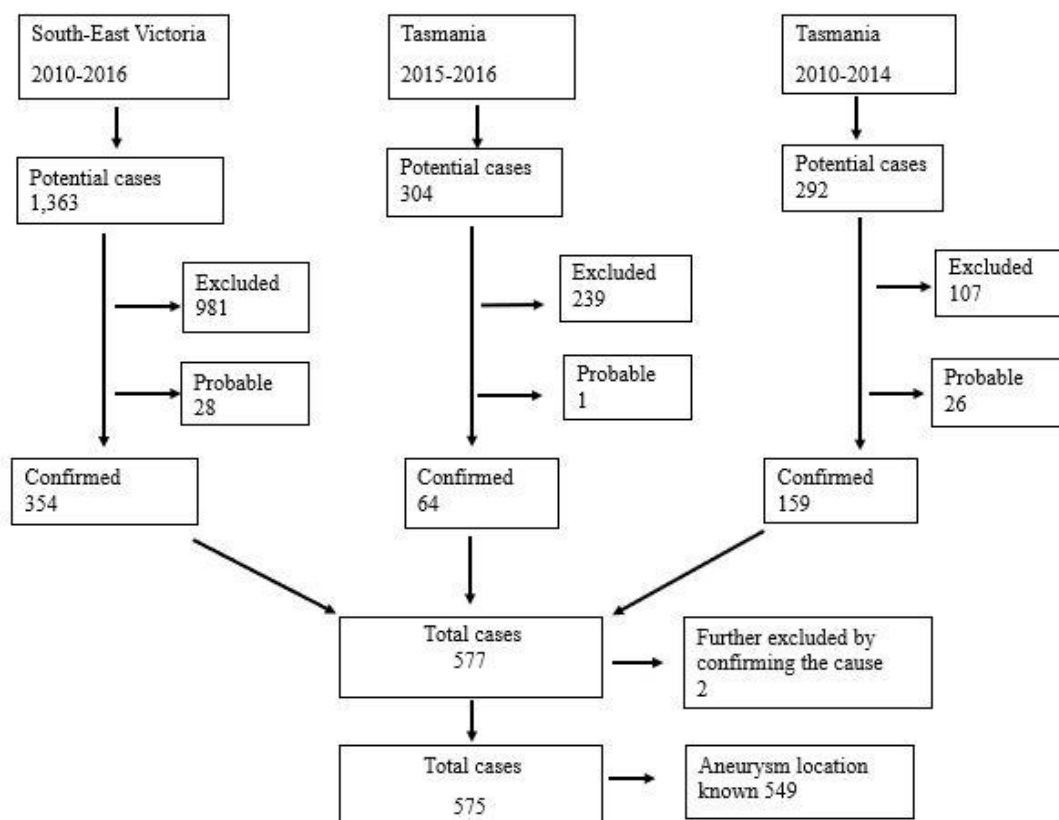
Figure 2-1 Flow chart showing the selection of participants for the REDDISH study

2.3.2 Demographics

There was 61% of the cohort from South-east Victoria and 31% from Tasmania. The median age of the 575 patients was 56 (IQR 46-67) years. Women were over-represented (69% of cases) and were older than men (median age 57 vs 55). There was no statistically significant difference between men and women for the demographic variables except for age, presented in **Table 2-1**.

Table 2-1 Sex differences in demographic factors in aSAH cohort of REDDISH study

	Total N=575	(%)	Men N=177	(%)	Women N=398	(%)	P-value
Age Mean (SD)	56 (15.29)		55 (15.10)		57 (15.33)		0.06
Charlson comorbidity score							0.22
0	415	(72)	136	(77)	279	(70)	
1 or 2	118	(20)	29	(16)	89	(22)	
>2	42	(7)	12	(7)	30	(7)	
WFNS							0.39
I	253	(44)	87	(49)	166	(42)	
II	99	(17)	27	(16)	72	(18)	
III	26	(4)	6	(3)	20	(5)	
IV	51	(8)	12	(7)	39	(10)	
V	134	(23)	43	(24)	91	(23)	
Missing	13	(2)	2	(1)	10	(3)	
Modified Fisher score							0.67
0	8	(1)	2	(1)	6	(2)	
1	50	(9)	17	(9)	33	(8)	
2	18	(3)	8	(4)	10	(2)	
3	111	(19)	37	(20)	74	(19)	
4	330	(57)	98	(55)	232	(58)	
Missing	58	(10)	15	(9)	43	(11)	
Hospital network							0.58
Victoria	354	(61)	106	(60)	248	(62)	
Tasmania	221	(39)	71	(40)	150	(38)	

2.3.3 Clinical variables

A large proportion of patients had a favourable grade of WFNS (WFNS I, 44%) on presentation and most had a severe grade of haemorrhage recorded on CT scan (modified Fished score 4, 57%). A comparison of severity scores is shown in **Figure 2-2**.
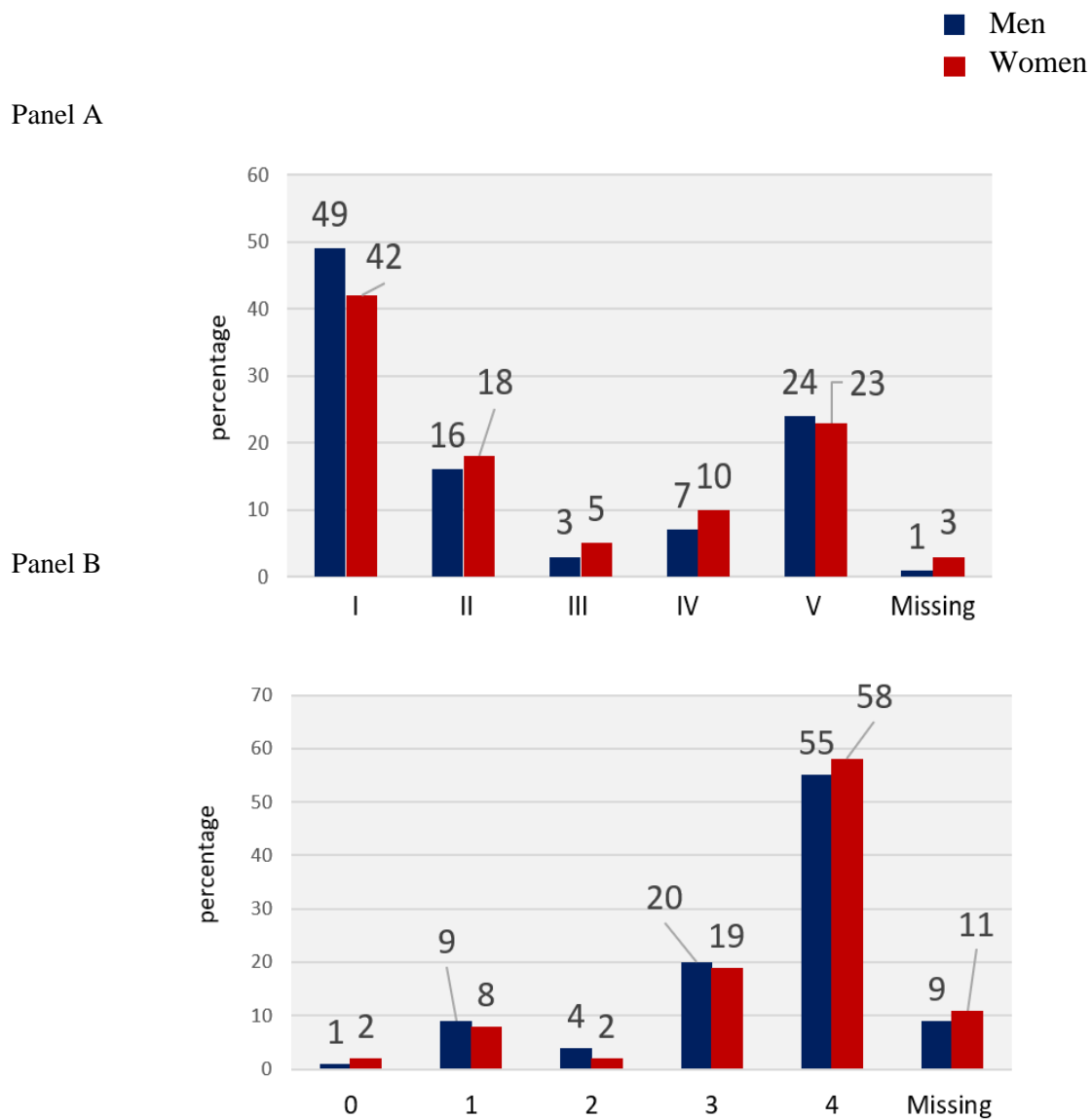
Panel A

Panel B

Figure 2-2 Comparison of World Federation of Neurological Surgeons grade (WFNS) (Panel A) and modified Fisher score (Panel B) between men and women

There were sex differences noted for only some risk factors. The risk factors like a family history of aSAH or aneurysm were not different by sex (**Table 2-2**). Comparing behavioural risk factors, heavy alcohol intake was more common in men than in women (20% vs 6%, p<0.001) and more men were current smokers (51% vs 43%, p=0.10) as shown in Table 2-2. Among cardiovascular risk factors, women were more hypertensive than men (31% vs 47%, p=0.008, **Table 2-2**).

Table 2-2 Sex differences in risk factors of aSAH

	Total N=575	(%)	Men N=177	(%)	Women N=398	(%)	P-value
Family history of aSAH							0.96
Yes	33	(5)	10	(6)	23	(6)	
No	247	(43)	74	(42)	173	(44)	
Missing	295	(51)	93	(52)	202	(51)	
Family history of brain aneurysm							0.11
Yes	24	(4)	4	(2)	20	(5)	
No	231	(40)	75	(42)	156	(39)	
Missing	320	(56)	98	(55)	222	(56)	
Smoking							0.10
Current smoker	261	(45)	90	(51)	171	(43)	
Ex-smoker	61	(11)	25	(14)	36	(9)	
Non-smoker	122	(21)	32	(18)	90	(23)	
Missing	131	(23)	30	(16)	101	(25)	
Alcohol							<0.0001
Light drinker	102	(17)	33	(19)	69	(17)	
Heavy drinker	60	(10)	35	(20)	25	(6)	
Ex-heavy drinker	8	(1)	3	(2)	5	(1)	
Non-drinker	71	(12)	13	(7)	58	(14)	
Missing	334	(58)	93	(52)	241	(60)	
Hypertension							0.008
Yes	248	(43)	61	(31)	187	(47)	
No	308	(53)	108	(64)	200	(50)	
Missing	19	(3)	8	(4)	11	(2)	
Cardiovascular disease							0.66
Yes	38	(7)	13	(7)	25	(6)	
No	497	(86)	153	(86)	344	(86)	
Missing	40	(7)	11	(6)	29	(7)	
Hypercholesterolemia							0.61
Yes	79	(14)	22	(12)	57	(14)	
No	457	(79)	145	(82)	312	(78)	
Missing	39	(7)	10	(5)	29	(7)	
Diabetes							0.79
Yes	30	(5)	10	(6)	20	(5)	
No	506	(88)	157	(88)	349	(88)	

	Total N=575	(%)	Men N=177	(%)	Women N=398	(%)	P-value
Missing	39	(7)	10	(6)	29	(7)	
Liver disease							0.76
Yes	11	(2)	3	(2)	8	(2)	
No	520	(90)	164	(93)	356	(89)	
Missing	44	(7)	10	(5)	34	(8)	

There were no significant sex differences detected in the use of medications that are a risk for aSAH (**Table 2-3**).

Table 2-3 Sex differences in medications as risk factors in aSAH cohort

	Total N=575	(%)	Men N=177	(%)	Women N=398	(%)	P-value
Anticoagulants							0.48
Aspirin	43	(7)	15	(8)	28	(7)	
Other	19	(3)	8	(4)	11	(3)	
No	506	(87)	153	(86)	353	(88)	
Missing	7	(2)	1	(0.5)	6	(2)	
Hormone replacement therapy							-
Yes	11	(2)	-	-	11	(2)	
No	314	(79)	-	-	314	(79)	
Missing	73	(18)	-	-	73	(18)	

2.3.4 Inter-hospital transfer

Regarding hospital referral for better management, it was also observed that 47% (n=268) of patients were transferred to a tertiary hospital while 52% (n=302) were admitted to first hospital they arrived at a tertiary care institute. No differences between men (admitted n=92, 52%; transferred n=84, 47%) and women (admitted n=210, 53%; transferred n=184, 46%) were observed (p=0.9) regarding inter-hospital transfer.

2.4 Discussion

This chapter describes the methods used to collect data in the REDDISH study that was used for this thesis. This is one of the largest multicentre cohorts of aSAH cases worldwide. There are very few existing studies in which a comprehensive number of variables have been captured regarding management and outcomes of aSAH. In this study, women were overrepresented and relatively older compared to men, similar to the previous studies. In this cohort, it was found that women more often had a history of hypertension compared to men, while alcohol intake

was more commonly observed in men than in women. This cohort of aSAH cases had data collected at two hospital networks and compares favourable to previously published studies with a smaller number of cases,[65, 79] that were single-centred,[52, 65] limited to certain geographical region[83] or group of aSAH patients, for example, only poor-grade[80] or good-grade patients who were eligible for treatment.[75]

The REDDISH cohort was similar to the other large cohorts of aSAH regarding key characteristics including demographics, vascular risk factors and severity scores. A comparison with best practice cohorts is described. In a recent prospective population-based study on 476 confirmed cases of aSAH (2007-2018) in Catalonia, the authors included treated patients in their study and observed the outcomes of death and disability following treatment procedure.[130] The data comprised of common risk factors, location of the aneurysm and neurological complications (DCI, hydrocephalus, rebleed). In that study, women were predominant (65%) and the median age of the cohort was 53 years. Vascular risk factors including hypertension were present in 41% and current smokers comprised 35% of the patients. Clinical score (Hunt and Hess) was better than the imaging score (Fisher grade). The majority of patients had Hunt and Hess grade 2 (45%) while on imaging, a more severe category of Fisher grade was noted in most of the patients (Fisher grade IV in 62%). Therefore, clinically, most patients did not have poor-grade haemorrhages, but imaging scores depicted that many patients had a severe stroke, like the findings in the REDDISH study. Overall, the characteristics of this cohort were similar to the REDDISH study. However, the investigators did not compare men and women in terms of management or outcome. Their study also has lesser detail regarding aneurysm characteristics and there is a lack of information on the standardisation of definitions of complications compared to REDDISH. Another example of a large study based on aSAH includes the multicentre Australasian Cooperative Research on Subarachnoid Haemorrhage Study (ACROSS) with 432 participants and a case cross-over design with cases recruited from 1995 to 1998.[131] The researchers scrutinized medical records, emergency departments, neurosurgery wards, medical wards, discharge records and death records to identify the cases of aSAH. Women comprised 62% and the mean age of the cohort was 57 years, which is strikingly similar to the REDDISH. Among vascular risk factors, 44% were hypertensive, 39% were current smokers, 12% were heavy drinkers and 4% were diabetic while severity scores were not reported. Despite the similarity in the characteristics of REDDISH and ACROSS cohort, some important variables regarding aSAH (aneurysm features and neurological complications) were missing from this study and sexes were not compared. Other large

prospective studies[132, 133] are comparable to REDDISH cohort regarding vascular and severity characteristics but with no information on sex differences, and missing details regarding standard definitions for neurological complications[132] or lack of long-term follow-up.[133] Therefore, it appears that the REDDISH cohort is representative of the aSAH population comparing favourably to other cohorts despite some differences in methods.

There are very few studies based on aSAH that have compared risk factors, clinical characteristics and outcomes between men and women. To understand how comparable REDDISH may be to the other studies that have been conducted, which may be important for generalisability, a brief comparison of REDDISH with other studies follows. Note that detailed analyses of the role of sex in aspects of care and outcome are described in chapter 4 and 5, with this section not intended to explore these associations in detail. In a large study including 617 patients with aSAH, authors examined the role of the female sex for poor functional outcome using modified Rankin scale (mRS 4-6) after aSAH at 3 months.[52] The authors studied sex differences in common risk factors (age, hypertension, alcohol, smoking, family history, diabetes mellitus), aneurysm characteristics (location, side and size), severity score (WFNS), type of management (surgery or endovascular) and complications (vasospasm, hydrocephalus). Women comprised 69% of sample size and the mean age of the cohort was 55 years, Age was the only risk factor that was different between the sexes (men 51 years vs women 56 years). Regarding vascular risk factors, no statistically significant difference by sex was noted. However, more women were hypertensive (men 26% vs women 32%) and current smokers (men 35% vs women 39%) while relatively more men than women were diabetic (men 10% vs women 7%). Alcohol consumption was similar in men and women (23% each). Regarding clinical severity score, the most common category was WFNS I (55%), a better clinical condition with no difference by sex observed. Limitations of that study included that it was a single-centred study and authors did not discuss imaging-based severity scores (e.g. modified Fisher score). Also, they only discussed vasospasm and hydrocephalus as complications and the definitions were not standardised. In another study including 120 cases of aSAH, a group of investigators compared sex difference in poor outcomes which included worse functional outcome (mRS 4-6) and mortality at 6 months.[65] The authors examined risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia), aneurysm characteristics (e.g. site) severity scores (with WFNS and Fisher grade), type of management (clipping/coiling) and complications (e.g. hydrocephalus by indication, vasospasm, rebleed). Women were predominant (69%) and the mean age of the cohort was 56 years. Women were older compared

to men (men 51 years vs women 58 years). Vascular risk factors including hypertension (men 37% vs women 28%) and current smoking (men 16% vs women 13%) were more common in men than in women while diabetes mellitus in women (men 0% vs women 1%). Dyslipidemia was similar in both sexes (13%). These risk factors were not different by sex. WFNS I (36%) and V (28%) were the most common grades of severity in the overall cohort with no difference by sex detected for this score. Imaging score Fisher grade 3 (79%) was the common category in this cohort with no sex difference noted for this scale. The limitations of the study included that it was a single institution-based study, the aneurysmal characteristics included were limited, and the definitions of complications were not standardised. Hence, in comparison to the previous studies focused on sex differences, REDDISH compares favourably.

In REDDISH, sex differences were noted in some vascular risk factors including hypertension history and alcohol intake but not for other known aSAH risk factors and severity scores. Of note is that missing data was a limitation for some of the variables. A comparison of aneurysm characteristics, neurological complications and evidence-based care between men and women is discussed in detail in Chapter 4 and 5 of this thesis. The comparison of severity scores between sexes has been examined in a few studies in which authors reported no difference by sex for WFNS and Fisher scores.[52, 65, 69] Rigorous examinations of sex differences between commonly used severity scores could be of importance in explaining differences in certain outcomes, for example, neurological complications like DCI. Modified Fisher predicts DCI and sex differences have been noted in this complication[88, 98] but no sex difference has been reported for this score. More studies are needed to examine the association of sex with these scores as this could help modify prediction of prognosis and management with an account of sex. Of note, there was a discrepancy between clinical severity score and imaging score in the REDDISH study, also observed in the previous studies.[65, 130, 134, 135] According to some investigators clinical scoring is more valid [134] and newly devised scores could be more useful to predict accurate prognosis.[134, 136]. Overall, the REDDISH study has an adequate sample size, a larger number of variables including risk factors, clinical characteristics with standardised definitions and long-term survival with which to examine the aims of this thesis.

2.4.1 Limitations and strengths

The data of the REDDISH study was retrospectively collected, which resulted in some missing data for the outcomes of interest (<10%) and risk factors like smoking (25%) after using alternate sources of information from digital medical records for incomplete information

regarding some variables. The retrospective design is most feasible because aSAH is rare (e.g. only 5% of all stroke types) and prospective studies would take considerable time to ascertain enough cases. For identification of aSAH cases, we used multiple overlapping data sources including emergency records, hospital admission records, imaging records to overcome any chance of missing a case from the study time-period. Incomplete data was present for a few outcomes of interest, for example, the site of the ruptured aneurysm was not always reported in medical records. Due to complete access to digital medical records, we were able to examine imaging reports and other records to identify the location of the ruptured aneurysm. The modified Fisher score was obtained using imaging records for any incomplete information with this completed by neuroradiologists. Important risk factor information (e.g. smoking) was sometimes missing, and to complete the information, medical history and operation theatre records were explored. Some risk factor information based on women-specific risk factors (age of menarche or age of pregnancy) could not be extracted due to the limitations of the retrospective study design. As the medical records were largely scanned written documents and not therefore entirely digital, this was a limitation while recording for some variables like vital signs of the patients and record of medications received while in hospital. We did not record for the route of medication administration. Regarding the treatment of hydrocephalus, we did not have adequate information to accurately control for this by indication and timing.

The results are only generalisable to hospitalized patients with aSAH. While in Tasmania we can identify out of hospital deaths due to the nature of the hospital network capturing the complete underlying island population, this is not possible for south-east Victoria. Note that out of hospital death data for Tasmania are not reported in this thesis due to the late arrival of these data. We also did not have any information on functional outcomes and quality of life scores due to the retrospective design of the study.

There were several strengths of the current study. It was a large cohort of first-ever aSAH conducted at two centres, with data recorded for all consecutive cases of radiographically confirmed aSAH. The data comprised of a large number of variables accessed through clinical and radiological records. Moreover, the study was not restricted to only 'good' grade or treated patients. Our use of standard definitions of neurological complications using NINDS criteria is also a strength. The data has a detail on the time of major events in the management of aSAH (for example, time of aSAH symptoms, time of ambulance and hospital arrival, time of treatment) which could be helpful to examine the delays occurring in aSAH treatment.

2.5 Conclusion

In conclusion, the REDDISH study comprises of a large number of variables collected from two geographical regions from multiple data sources using digital medical records. The information was recorded on the time of various events occurring from the start of the event of aSAH to the outcome at discharge and 1 year. Detailed information on the management of aSAH, symptoms, treatment, complications and their management, and outcomes were recorded which has not been observed in most of the previous studies of aSAH. This makes REDDISH a valid data set with generalisable results with which to examine sex differences in this condition.

Chapter 3: Sex differences in Risk factors for Aneurysmal Subarachnoid Haemorrhage: Systematic Review and Meta-analysis

3.1 Preface

This thesis chapter has been published as a paper in the *Journal of the Neurological Sciences* (see Appendix C)

Authors note - There are some differences between this chapter and the published version of this manuscript due to integrating supplements to assist with readability of the thesis.

3.2   Abstract

Background: Aneurysmal subarachnoid haemorrhage (aSAH) disproportionally affects women. We conducted a systematic review and meta-analysis to explore sex differences in aSAH risk factors.

Methods: Case-control/cohort studies were searched to November 2017 with sex-specific risk factors for aSAH. Meta-analysis was performed when a risk factor was reported in ≥2 studies.

Results: Of 31 studies, 22 were eligible for meta-analysis. Female sex was associated with greater odds of aSAH ($HR_{adjusted}$ 1.90 [1.47-2.46]. There was no detectable difference between the sexes for hypertension ($OR_{adjusted}$: men 3.13 [2.26-4.34]; women 3.65 [2.87-4.63], p=0.18), smoking ($OR_{adjusted}$: men 2.96 [1.68-5.21]; women 3.11 [1.21-7.97], p=0.95), aSAH family history, systolic blood pressure, age and some genetic variations. Alcohol ($OR_{adjusted}$: men 1.50 [1.04-2.17]; women 0.83 [0.48-1.45], p=0.003), high alanine aminotransferase levels, and some gene variants increased the risk of aSAH in men. Reproductive factors, divorce and some genetic variations increased the risk in women. High aspartate aminotransferase levels in men and, diabetes ($OR_{adjusted}$: men 0.57 [0.32-1.01]; women 0.24 [0.13-0.43], p=0.01) and parity in women reduced aSAH risk.

Conclusion: We recommend sex-specific re-analysis of existing studies of aSAH risk factors. Known aSAH risk factors (hypertension, smoking and alcohol consumption) should be targeted to prevent aSAH in men and women.

3.3 Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) occurs more often in women than in men[43, 137] but the reasons for this are unclear. SAH results from the rupture of an aneurysm in approximately 85% of cases.[138] Of note, the prevalence of unruptured intracranial aneurysms is higher in women compared to men (4.4 vs 2.5%)[46] consequently increasing the risk of rupture. The risk factors for aSAH are likely to be distinct from other causes of SAH, but few studies have been conducted to explore sex differences in risk factors for aSAH. In a systematic review on risk factors for SAH, Tiunissen et al did not detect sex differences in alcohol consumption, cigarette smoking and hypertension.[48] Feigin et al conducted an updated systematic review of SAH, and reported that hypertension and alcohol intake were more hazardous in women while hypercholesterolemia reduced the risk of SAH in men, although none of these risk factors were statistically different between women and men.[49] These reviews included studies with varied designs (e.g. clinical trials, case-crossover studies, etc), were not focussed on exploring sex differences, and included only a limited number of risk factors. In addition, these reviews did not include examination of sex differences in genes associated with the risk of aSAH.

Our aim was to conduct a comprehensive review of sex differences in risk factors for aSAH to explore the reasons for the greater incidence in women than men.

3.4 Methods

3.4.1 Literature sources and search strategy

Pubmed, Scopus, Medline via Ovid and Embase via Ovid were searched from inception to Nov 27, 2017. The **Appendix A** provides the full search strategy. Keywords and medical subject headings used for searching the databases included "sex characteristics", "sex difference", "gender difference", "sex based", "sex distribution", "sexual dimorphism" AND "aneurysmal subarachnoid haemorrhage", "ruptured cerebral aneurysm", "ruptured intracranial aneurysm", "ruptured brain aneurysm" AND "risk factors". The review was registered with PROSPERO (ID: CRD42018091521). Studies focused specifically on cohorts of women or case-control studies with women only were examined.

3.4.2 Study screening for title and abstract

Two reviewers (SR and BWS) screened titles and abstracts based on the following inclusion criteria: (1) cohort, case-control, cross-sectional, case series or case-reports at least 10 cases,

(2) provided details of stroke subtypes or subarachnoid haemorrhage and risk factors, (3) mentioned sex differences in risk factors or were women specific studies but with risk factors not limited to only women like smoking or hypertension (4) were published in English. Studies were excluded if they were 1) animal-based, experimental, autopsy series, or included fewer than 10 patients, or 2) included non-aneurysmal SAH, either on its own or as a combined category with aSAH.

3.4.3 Full text screening

For full-text screening, a study was included when: (1) It was a cohort or case-control study, (2) included aneurysmal subarachnoid haemorrhage, had criteria indicating that history and CT findings were highly suggestive of aneurysmal origin, and did not provide evidence of inclusion of SAH other than aneurysmal rupture, (3) provided effect estimates with 95% CI or raw data to calculate these, included risk factors that were stratified by sex, or included an interaction term between sex and risk factors for aSAH.

3.4.4 Risk of Bias and Methodological quality assessment

Two independent reviewers (SR and MD) used Newcastle-Ottawa Quality Assessment Scale[139] for case-control and cohort studies to assign level of quality to each study. This scale has a range from 0-9 and was modified for this review. Any conflict between the two reviewers was resolved by discussion. Quality Assessment Newcastle Ottawa scale was used for quality assessment of the studies included in the review. Few questions were modified for the review. In definition of case for case-control study scale and, in assessment of outcome for cohort studies; addition of secure records like imaging techniques was added in the section. Objective measurement was added to ascertainment of exposure in both case-control and cohort studies and a star was awarded if any risk factor was measured objectively in a study (**Table 3-1** and **Table 3-2**).

3.4.5 Data Extraction

Reviewers (SR and MD) independently extracted predefined data items (see Supplementary Methods). If a study provided more than one adjusted estimate, the fully adjusted estimate was extracted. If two or more studies provided effect estimates for a given risk factor, it was included in the meta-analysis.

Extracted items included: author, year of publication, study period, study design, sample size for cohort or cases and controls for case-control study, male and female cases and controls or

sample size, follow up period for cohort studies, mean age, risk factors, effect estimates crude or adjusted for different risk factors in men and women, covariates adjusted in the study, and any potential reason provided by the authors for the identified difference between the sexes.

Risk factors such as smoking, and alcohol consumption were analysed by exposure categories when available. For smoking, we included studies that were not stratified by smoking status or provided combined current and former smokers' estimates. For alcohol consumption, we included estimates for drinkers compared to non-drinkers in the meta-analysis, but not different categories of alcohol consumption as they varied across the studies.

Table 3-1 Newcastle Ottawa scale (modified version) for case-control studies

Newcastle Ottawa scale (modified version) for case-control studies		
Selection		Total stars awarded
1) Is the case definition adequate?	a) yes, with independent validation (information extracted from record or reference to record source like imaging) *	
	b) yes, example record linkage or based on self-reports	
	c) no description	
2) Representativeness of the cases	a) cases with outcome of interest in a defined period of time and in a defined catchment area *	
	b) potential for selection biases or not stated	
3) Selection of Controls	a) community controls *	
	b) hospital controls	
	c) no description of source	
4)Definition of control	a) no history of disease(endpoint)*	
	b) no description of source	
Comparability		
1) Comparability of cases and controls on the basis of the design or analysis	a) study controls for age *	
	b) study controls for any additional factor like hypertension, smoking or any covariates mentioned in the study*	
Exposure		
1) Ascertainment of exposure	a) objective measurement*	
	b) Hospital records where exposure to risk factors completed by medical staff/blood tests recorded/population registries*	
	c) structured interview where blind to case/control status *	
	d) interview not blinded to case/control status	
	e) written self-report	
	f) no description	
2) Same method of ascertainment for cases and controls	a) yes*	
	b) no	
3) Non-Response rate	a) same rate for both groups *	
	b) non-respondents described	
	c) rate different and no designation	

A study can be awarded a maximum of one star (*) for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability.
0.5* for providing the catchment area, but no definite time-period.

Table 3-2 Newcastle Ottawa scale (modified version) for cohort studies

Newcastle Ottawa scale (modified version) for cohort studies		
Selection		Total stars awarded
1)Representativeness of the exposed cohort	a) Truly representative of the average in the community (Consecutive or non-consecutive participants were selected or invited to participate from the source population) *	
	b) somewhat representative of the average in the community or population source *	
	c) selected group of participants	
	d) no description	
2) Selection of the non- exposed cohort	a) drawn from the same community as the exposed cohort*	
	b) drawn from a different source	
	c) no description of the derivation of the non-exposed cohort	
3) Ascertainment of exposure	a) Objective measurement*	
	b) Hospital records completed by medical staff (measurement on physical examination or information collected by medical staff)*	
	c) structured interview*	
	d) written self-report	
	e) no description	
4) Demonstration that outcome of interest was not present at start of study	a) yes*	
	b) no	
Comparability		
Comparability by controlling for confounders	a) study controls for age *	
	b) study controls for any additional factor like hypertension, smoking or any covariates mentioned in the study*	
Outcome		
1) Assessment of outcome	a) independent blind assessment or by reference to secure records imaging data including CT or DSA or LP*	
	b) record linkage*	
	c) self-report	
	d) no description	
2) Was follow-up long enough for outcomes to occur	a) yes*	
	b) no/not report	
3) Adequacy of follow up of cohorts	a) Complete follow up, all participants accounted for*	
	b) Subjects lost to follow up unlikely to introduce bias (<20% lost to follow up, or description provided of those lost) *	
	c) Follow up rate <80% and no description of those lost provided	
	d) no statement	

A study can be awarded a maximum of one star (*) for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability.

0.5* for mentioning the reason of loss to follow up but not providing the numbers of participants lost to follow up

3.4.6 Data Analysis

Crude and adjusted odds ratios (OR), risk ratios (RR), or hazard ratios (HR) were reported for different risk factors for aSAH for men and women. Random-effects meta-analysis was used to pool estimates by approximating OR and RR for available studies. Subgroup analysis was performed by comparing the pooled results of similar studies for a risk factor in men and women. We included studies in the analysis in which aneurysm was further confirmed by angiography, MRA (Magnetic Resonance Imaging), DSA (Digital Subtraction Angiography), during surgery or at autopsy and, performed sensitivity analysis for the studies which did not mention gold standard imaging methods or techniques for confirmation of the aneurysm. The mvmeta[140] command was used to conduct multivariate meta-analysis to test statistical significance of sex difference for the risk factors in those studies with stratified estimates. We also performed meta-regression between regions of low and high incidence of aSAH. Data analysis was conducted using Stata 15 (StataCorp LLC, Texas, USA). Begg's test was used to assess publication bias and p-value <0.05 was considered as significant.

3.5 Results

From 12,864 records, 50 potential studies including two abstracts (case-control studies=42, cohort studies=8) on risk factors for aSAH were identified (**Figure 3-1).** Among 31 studies of sex differences in aSAH, two of which were abstracts (case-control studies=27, cohort studies=4), there were a total of 8,611 cases in 27 case-control (n=7,726) and 4 cohort (n=885) from 15 countries. We could not include 19 studies (case-control studies=15, cohort studies=4) as no sex specific results were reported by the authors. Most of the studies were from Japan (n=6) and Sweden (n=6), followed by Norway (n=3), and the United States of America (n=3). All case-control studies were of high quality, with score ≥6 except one, which was an abstract. Three out of four cohort studies were of high quality with scores ≥6. No evidence of publication bias was found.

3.5.1 Risk Factors and Risk of Bias and Methodological quality assessment scores

A summary of all the risk factors across the studies is provided in **Table 3-3, Table 3-4** and **Table 3-5** details are explained below. The quality assessment scores of included studies are provided in **Table 3-6** and **Table 3-7**.

Identification

Records identified through database searching (n=12,857)

Pubmed (3,252), Embase via ovid (4,938), Medline via ovid (2,248), Scopus (2,214)

Additional records identified through other sources (n =7)

Screening

Records after duplicates removed (n =8,339)
Grey literature (7)

Records excluded (n=7,442)

Records screened (n=8,406)

Full-text articles excluded, with reasons (n=923)

392 do not specifically mention aSAH
157 Wrong study design
111 gender distribution not defined in population
63 foreign language
90 Wrong outcomes
44 reviews
25 duplicates
15 Wrong setting
8 fewer than 10 cases
6 letters to editor
5 comments
4 autopsy studies
2 restricted to one artery
1 no abstract or full text available

Eligibility

Full-text articles assessed for eligibility (n=973)

Potential studies identified (n=50)

Included

Studies excluded for not providing sex differences for risk factors (n=19)

Studies included in quantitative synthesis (meta-analysis) (n=22)

Studies included in qualitative synthesis (n=31)

Figure 3-1 Flow chart showing the selection of the studies included

Table 3-3 Risk factors identified from cohort and case-control studies

Risk Factors	Number of Cohort studies studies		Number of Case-Control studies	
Women-specific	**Number of studies**	**Number of cases (%women)**	**Number of studies**	**Number of cases (%women)**
Female sex	2	160(67)[†]	7	2,239 (63)[†]
Age at menarche	1	76	1	124
Parity	1	78	2	405
Age at first pregnancy			1	124
Menstrual cycle regularity			1	124
Menopause status	1	79	1	124
Age at first childbirth			1	124
Gravidity			1	124
Marital status	1	185		
HT use	1	58		
aSAH predilection area	1	44		
OCPs use	1	N/A	1	4
Common in both sexes				
Smoking	1	120(66)	12	1,631(48)[††]
Blood Pressure/SBP	1/1	89(48)/120(66)	7	811(61)[††]
Hypercholesterolemia			3	283(74)
Hypertriglyceridemia			1	7(71)
Diabetes Mellitus			3	62(51)
Alcohol intake	1	119(66)	5	649(25)[††]
Liver Disease			1	18(33)
CAD			2	114(71)
Family History	1	37(73)	1	29(62)
Migraine			1	1

Stress (Work or children related)			1	380(66)
AST			1	38(60)
ALT			1	33(42)
UN			1	54(55)
ADAMST13 polymorphism			1	183(74)
GpIIIa A1/A2 polymorphism			1	201(44)
FXIII VARIANT H2 & H3			1	183(74)
Genotype II of the ACE gene			1	90(63)
NOS3 27-bp-VNTR b/b genotype			1	333(70)
Genetic variation on 9p21			1	183(74)
Age	1	120 (66)	1	120 (66)
Cold temperature			1	1(N/A)
	Total =34			

ADAMST13: A Disintegrin-like and Metalloprotease with
Thrombospondin Type1 Motif, 13, ALT: Alkaline aminotransferase, AST: Aspartate aminotransferase
Gp: Glycoprotein, HT: Hormonal Therapy, FXIII; clotting factor XIII, ACE; Angiotensin Converting Enzyme, NOS; Nitric Oxide synthase, OCPs:
Oral contraceptives, UN: Urea Nitrogen
VNTR; variable number tandem repeat
† %age of women against men
†† %age for women is average of sex-specific data provided by some of the studies

Table 3-4 Case-control studies: Risk factors in included studies

Study	Year	Country	Study Years	Cases of aSAH	Risk Factors	Assessment of Risk Factors
Adamski et al[141]	2009	Poland (Krakow)	2001-2007	288	GpIIIa A1/A2 polymorphism, Female sex	PCR, RFLP
Anderson et al [142]	2004	Australia (Adelaide, Hobart, and Perth) & New Zealand (Auckland)	1995-1998	330	Past, current and never smoking	Structured in person interview with standardized questionnaire & Medical records
Bell & Symon[143]	1979	United Kingdom (London)	1965-1978	208	Smoking	Hospital records verified by postal questionnaire
Can et al[144]	2017	United States of America (Boston)	1990-2016	1302	Female sex	Medical records
Canhao et al[145]	1994	Portugal (Lisbon)	1985-1990	141	HTN, Tobacco use, DM, High cholesterol High triglycerides	In person interview & measurement of Blood pressure, fasting glucose
de Wilde et al[146]	2013	Netherlands (Utrecht)	not given	490	Stress related events in life (work and children)	Self-report
Gaist et al[147] #	2004	Sweden	1973-1997	281	Parity, Smoking prior to first child birth	Birth, in-patient & cause of death registries
Hanson et al[148]	2013	Sweden (Gothenburg)	not given	183	Genetic variation at ADAMTS13	Genotyping

Study	Year	Country	Study Years	Cases of aSAH	Risk Factors	Assessment of Risk Factors
Inagawa[149]	2005	Japan (Izumo)	1980-1998	247	HTN, DM, CAD, Liver disease, High cholesterol, Current regular & former smoking, Daily drinker, AST level >40iu/l, ALT level >35iu/l & Urea Nitrogen level >20mg/dl	Medical history and serum levels
Inagawa[150]	2010	Japan (Izumo)	1981-2005	858	HTN, DM, CAD, High cholesterol, Current, regular & former smoking, Daily drinker	Medical history (disorders and lipid lowering medication), and serum levels
Jimenez-yepes et al[151]	2008	Colombia (Medellin & Cali)	2004-2005	163	Female sex	Hospital records
Juvela et al[152]	1993	Finland (Helsinki)	not given	278	HTN, Alcohol intake (recent), former and current smoking	In person interview with structured questionnaire
Kowalski & Nyquist [153]	2015	United States of America (Baltimore, Maryland)	1993-2009	933	Female sex, cold temperature	Hospital records
Koshy et al [95]	2010	India (Kerala)	2003-2008	163	HTN, Smoking, Alcohol intake	Self-report
Kubota et al[154]	2001	Japan	not given	127	Smoker, Drinker	Self-report
Ladenvall et al[155]	2009	Sweden (Gothenburg)	2000-2004	183	FXIII haplotypes H2-H6, SNP Leu34 allele carriers	Genotyping
Morris et al[156]	1992	England (Liverpool)	1990	144	Smoking	Hospital records

Study	Year	Country	Study Years	Cases of aSAH	Risk Factors	Assessment of Risk Factors
Okamoto et al[157]	2001	Japan (Nagoya)	1992-1997	195	Age at menarche, Parity, Age at first pregnancy, Menopausal status, Menstrual cycle regularity, Age at first child birth, Parity, Gravidity	In person interview with structured questionnaire
Okamoto et al[158]	2003	Japan (Nagoya)	1992-1997	201	Family history	In person interview with structured questionnaire
Okamoto et al[159]	2005	Japan (Nagoya)	1992-1997	124	HTN, Smoking	In person interview with structured questionnaire
Olsson et al[160]	2010	Sweden (Gothenburg)	2000-2004	183	Genetic variation on 9p21	Genotyping
Pettiti & Wingerd [161#]	1978	United States of America (California)	1969-1971	11	Current OCP use, Smoking, HTN, Migraine history	Self-report &/or PE
Ruiz-Sandoval et al[162]	2009	Mexico	2002-2004	231	Female sex	Medical records & standardized questionnaire
Slowik et al[163]	2004	Poland (Krakow)	2003-2004	90	b/b genotype of intron-4 27bp VNTR polymorphism, Female sex	PCR & Hospital records
Staalso et al[164]	2014	Denmark (Copenhagen)	2006-2011	333	Genotype II of the ACE gene, Female sex	Genotyping
Vlak et al[165]	2013	Netherlands (Utrecht)	2006-2009	250	HTN, Smoking, Family history, High cholesterol	Medical records & questionnaire
You et al[166 #]	2010	South Korea (Seoul)	1995-2006	167	Female sex	Hospital records

Nested case-control studies; Abbreviations: ACE: Angiotensin converting enzyme, ADAMTS13: A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif, 13, ALT: Alkaline aminotransferase, AST: Aspartate aminotransferase, CAD: Coronary artery disease, DM: Diabetes Mellitus, FXIII: Factor XIII, GpIIIa; Glycoprotein IIIa, HTN: Hypertension NOS3; Nitric oxide synthase gene, OCP: Oral contraceptive pill, PCR: Polymerase chain reaction, RFFLP: Restriction fragment length polymorphism, SNP: Single nucleotide polymorphism, VNTR: Variable number of tandem repeats

Table 3-5 Cohort studies: Risk factors in included studies

Author	Year of Publication	Country	Study Years	Cases of aSAH (cases/person yr)	Risk Factors	Assessment of Risk Factors
Lindekleiv et al [94]	2011	Norway (Nord-Trøndelag County & Tromso)	1994 - 1997	120 (14.6/100,000 person-years in women & 8.8100,000 person-years in men)	Age, HTN, SBP, Smoking, Alcohol, Family history, Age at menarche, Menopausal status, HT use, Parity	Self-report & Physical examination
Lindegard et al [167]	1987	Sweden (Gothenburg)	1970-1979	551	SAH predilection area & marital status	Medical records
Sandvei et al [168]	2009	Norway (Nord-Trøndelag County & Tromso)	1984-2005	132 (9.9/100,00 person-years)	Female sex	Physical examination, blood samples, self-report
Sandvei et al [169]	2012	Norway (Nord-Trøndelag County & Tromso)	1994-2007	122 (122/977895 person-years)	Female sex	Physical examination, blood samples, self-report

Abbreviations: HTN: Hypertension, HT: Hormone therapy, SBP: Systolic blood pressure

Table 3-6 Quality assessment of Case-control studies

Included studies	Total score (9)	Selection				Comparability		Outcome		
		Case def.	Repr. of cases	Control Selection	Def. of control	Comp. of cases and controls		Ascertain. of exposure	Method of ascertain. for cases and controls	Non-Response rate
Adamski et al[141]	9	*	*	*	*	*	*	*	*	*
Anderson et al[142]	8	*	*	*	*	*	*	-	*	*
Bell & Symon[143]	6	*	*	-	*	*			*	*
Can et al[144]	8	*	*		*	*	*	*	*	*
Canhao et al[145]	8	*	*	*	*	*	*	*	*	
deWilde et al (abst)[146]	4	-	-	-	-	*	*	-	*	*
Gaist et al[147]	9	*	*	*	*	*	*	*	*	*
Hanson et al[148]	8.5	*	* (1/2)	*	*	*	*	*	*	*
Inagawa (2005)[149]	8	*	*		*	*	*	*	*	*
Inagawa (2010)[150]	9	*	*	*	*	*	*	*	*	*
Jimenez-Yepes & London˜oFerna´ndez[151]	8	-	*	*	*	*	*	*	*	*
Juvela et al[152]	7.5	*	*(1/2)	-	*	*	*	-	*	*
Koshy et al[95]	7	*	*		*	*	*		*	*
Kowalski and Nyquist (abst)[153]	8	-	*	*	*	*	*	*	*	*
Kubota et al[154]	7	*	*		*	*	*		*	*
Ladenvall et al[155]	8	*	*	*	*	*	*	*	*	
Morris et al[156]	7	*	*	*	*	*			*	*
Okamoto et al (2001)[157]	8	*	*	*	*	*	*	-	*	*
Okamoto et al (2003)[158]	8	*	*	*	*	*	*	-	*	*
Okamoto et al (2005)[159]	8	*	*	*	*	*	*	-	*	*
Olsson et al[160]	8	*	*	*	*	*	*	*	*	-
Petitti & Wingerd[161]	6	*	-	-	*	*	*	-	*	*
Ruiz-Sandoval et al[162]	8	*	*	*	*	*	*		*	*
Staalso et al[164]	9	*	*	*	*	*	*	*	*	*
Slowik et al[163]	9	*	*	*	*	*	*	*	*	*

Vlak et al[165]	8	*	*	*	*	*	*		*	*
You et al[166]	9	*	*	*	*	*	*	*	*	*

Table 3-7 Quality Assessment of Cohort studies

Included studies	Total score (9)	Selection				Comparability		Outcome		
		Repr. of the expos. Cohort	Selection of the non-exposed cohort	Ascertain. of exposure	Absence of outcome at study start	Study controls for Confound.		Assessment of outcome	Length of follow up	Adequacy of follow up
Lindekleiv[94]	8.5	*	*	*	*	*	*	*	*	*1/2
Lindegard[167]	5	*	*	-	*	-	-	*	*	-
Sandvei (2009)[168]	9	*	*	*	*	*	*	*	*	*
Sandvei (2012)[169]	8.5	*	*	*	*	*	*	*	*	*1/2

Female sex

The association between sex and the risk/odds of aSAH was examined in eight case-control and two cohort studies (OR_{crude} range: 0.64-2.30, $OR_{adjusted}$ range: 0.69-2.13 for case-control studies; HR_{crude} 1.7 in one cohort study, $HR_{adjusted}$ 1.9 in two cohort studies). See **Table 3-8** and **Figure 3-2.** Crude estimates were reported in three case-control studies, [144, 164, 166] and one cohort study [169] while adjusted estimates were reported in six case-control studies [141, 144, 151, 153, 162, 163] and two cohort studies.[168, 169] Sensitivity analysis was performed for the studies that did not use gold standard imaging techniques for aneurysm confirmation, but results did not vary after excluding them.

Women-specific risk factors

We observed women-specific risk factors for aSAH across different studies. See **Table 3-9.** In two studies, authors examined risk or odds of aSAH associated with age at menarche. Menarche at age <13 years was a risk factor for aSAH in multivariable analysis in one case-control study. [157] In a cohort study, compared to menarche at age 12-13; menarche at <12 years or >13 years was not a risk factor for aSAH.[94]

There was one case-control study on irregular menstrual cycle which showed that it was not a risk factor for aSAH.[157]

Parity was reported as a risk factor for aSAH by two case-control studies and one cohort study. In one case-control study, authors reported that increasing parity moderately reduced the risk for aSAH.[147] The authors in this study categorized parity from primiparous to multiparous with ≥5 childbirths and found inverse association of risk with increasing parity. Similar findings were reported in another case-control study where nulliparity significantly increased the risk when parity≥1 was taken as a reference.[157] In a cohort study, nulliparity and multiparous women with >3 children were not associated with any association for aSAH when parity with 1-3 children was taken as a reference.[94] One case-control study observed that first childbirth at ≥26 years was not associated with a risk for aSAH.[157]

One case-control explored the risk of nulligravidity when being gravida with of ≥1 children was a reference and observed an increased risk for aSAH.[157] In the same case-control study, first pregnancy at age ≥26 years was a risk factor for aSAH.[157]

Two studies mentioned oral contraceptive pills (OCPs) as a risk factor. One case-control examined current and past OCPs use as a risk factor for aSAH. An increased risk for aSAH

was observed which was further accentuated in smokers.[161] One cohort study proposed that high dose OCPs could be a risk for aSAH in young women but did not further explore an association for aSAH.[167] One cohort study examined hormone replacement (HT) as a risk factor, it was reported that HT use is not associated with a risk of aSAH.[94]

Two studies explored association of pre or post-menopausal women and aSAH. In one case-control did not find pre-menopause as a risk factor for aSAH when post-menopausal were taken as a reference.[157] While in cohort study, authors did not find post-menopause to increase the risk for aSAH when pre-menopausal women were a reference group.[94]

One cohort study examined marital status and found that being divorced increased the risk for aSAH in women but not in spinsters, widowed and married women.[167] In the same study, authors reported that women living in aSAH predilection; which were the three districts in Gothenburg (Sweden) with most of the young population, with an increased number of divorcees and strikingly high number of cases of aSAH area, also increased the risk.[167]

Smoking

Current smoking

All studies of the association between smoking and aSAH in men and women were of high quality. See **Table 3-10, Figure 3-3** and **Figure 3-4**. One cohort study reported crude risks for men (RR 3.47) and women (RR 6.50)[94] and six case-control studies[95, 143, 145, 154, 156, 159] provided crude estimates for comparing sex difference for smoking quantitatively in subgroup analysis. The OR_{crude} ranges in men (1.20-7.03) and women (1.93-5.70), and the $OR_{adjusted}$ ranges in men (1.1-6.08) and women (0.59-7.70) were similar. For pooled $OR_{adjusted}$, there were four case-control studies[142, 149, 150, 159] for both sexes. Multivariable meta-analysis provided no evidence of sex difference for smoking (OR_{crude} p=0.984 and $OR_{adjusted}$ p=0.95).

Two case-control studies [142, 152] provided risk of aSAH associated with current smoking stratified by dose. In both studies heavier smoking was associated with increased risk of aSAH in both sexes compared to low dose of smoking but more so in women than men.

Other smoking exposures

Former smoking

Three studies (two case-control and one cohort)[94, 142, 152] reported past smoking as a risk factor See **Table 3-10** and **Figure 3-5**. The $OR_{adjusted}$ for case-control studies ranged from 0.60-1.57

for men and 0.49-1.70 for women. Two case-control studies[142, 152] were eligible for meta-analysis. The pooled $OR_{adjusted}$ was 0.93 (95%CI 0.36-2.30) in men and 0.98 (95% CI 0.29-3.30) in women, thus, no association was observed in both sexes. No sex difference in risk of aSAH associated with former smoking compared to non-smoking or current smoking was observed in multivariate meta-analysis between men and women (p=0.97). The crude risk in one cohort study did not show any risk with either sex.[94]

One study classified former smoking according to years passed since quitting (1-4 years, 4-15 years and >15 years). No difference in risk of aSAH was observed in either sex.[142]

Non-smokers exposed to environmental tobacco smoke (ETS) had a different risk of aSAH to those not exposed in both sexes.[142] Ever smoking compared to never smoking was associated with a higher risk of aSAH in women but not men.[95]

Alcohol consumption

Six studies (five case-control studies and one cohort study) provided evidence for an association between alcohol consumption and risk or odds of aSAH (OR_{crude} range: men 2.20-2.62; women 1.90-4.0, $OR_{adjusted}$ range: men 1.50-1.52; women, 0.80-0.95). See **Table 3-11, Figure 3-6** and **Figure 3-7**. In meta-analysis, two case-control studies [95, 154] were included for pooled crude estimates and two case-control studies [149, 150] for pooled adjusted estimates In multivariate meta-analysis, OR_{crude} was not different between sexes (p=0.94), while for $OR_{adjusted}$ there was evidence for a stronger effect of alcohol consumption on men than women (p=0.003). In one cohort study, authors did not report any association of alcohol consumption as a risk factor in both sexes.[94]

One case-control study [152] categorised alcohol consumption within 24 hours (1-40gms, 40-120 gms, >120gms), and within one week (1-150gms, 150-300gms, >300gms) of the aSAH. Alcohol intake of 41-120gms within 24 hours, and >300gms was a risk for aSAH in both sexes but greater in women.

Blood Pressure

Blood pressure was examined as a risk factor for aSAH in eight studies (seven case-control and one cohort) with measures including hypertension [94, 95, 145, 149, 150, 152, 159, 161] and systolic blood pressure.[94] See **Table 3-12, Figure 3-8** and **Figure 3-9**.

In meta-analysis, four case-control studies [95, 145, 152, 159] were included for pooled crude estimates and four case-control studies [95, 149, 150, 159] for pooled adjusted estimates (OR_{crude} range: men 1.75-5.40; women 1.68-7.67, $OR_{adjusted}$ range: men 2.75-4.40; women 3.28-4.86). The results of multivariate meta-analysis provided no evidence of sex difference for hypertension (OR_{crude} p=0.82, $OR_{adjusted}$ p=0.18).

Increase in SBP was equally a risk for aSAH in both sexes in a cohort study (HR: men 1.23; women 1.16).[94]

Diabetes Mellitus (DM)

Three case-control studies observed the association of DM and risk of aSAH in both sexes (OR_{crude} men 1.00; women 12.39, $OR_{adjusted}$ range: men 0.55-0.72; women 0.17-0.26). See **Table 3-13** and **Figure 3-10.** The OR_{crude} was reported in one study.[145] For meta-analysis, two studies were included. [149, 150] Diabetes mellitus was more protective in women than in men (p=0.01) as evident from multivariate meta-analysis.

Coronary artery disease (CAD)

CAD was assessed a risk factor in two high-quality case-control studies ($OR_{adjusted}$ range: men 0.44-0.92; women 0.33-1.34). See **Table 3-14** and **Figure 3-11**. Two studies were included for meta-analysis.[149, 150] No risk for aSAH was detected in either sex. In multivariate meta-analysis, no sex difference was observed for the risk of aSAH was associated with CAD (p=0.87).

Hypercholesterolemia and hypertriglyceridemia

There were three case-control studies examining hypercholesterolemia as a risk factor for aSAH in both sexes. See **Table 3-15** and **Figure 3-12**. (OR_{crude} men 0.53; women 1.15, $OR_{adjusted}$ range: men 0.89-2.47; women 0.73-3.49). The included studies were of high quality. The OR_{crude} was reported in one study.[145] Two studies were included for meta-analysis [149, 150] and no association was observed for the risk of aSAH. In multivariate meta-analysis, there was no detectable sex difference for hypercholesterolemia as a risk for aSAH (p=0.88).[145] For hypertriglyceridemia, $OR_{crude\ in}$ men was 0.64 and in women was 1.00 and was not found to be a risk factor in either sex in a case-control study.[145]

Family history

Family history was analysed as a risk factor for aSAH in one case-control and one cohort study. See **Table 3-16.** In the case-control study, family history of aSAH was found to be an equally

significant risk factor in both sexes. In the same study odds of aSAH associated with parental history of aSAH differed according to the sex of the parent. Positive maternal ($OR_{adjusted}$ 5.4, 95% CI; 1.8-16.0) and paternal history ($OR_{adjusted}$ 3.8, 95% CI; 1.1 to 13.4) were observed to be a risk factor, but only maternal history was significant in adjusted analysis.[158] In the cohort study, odds of aSAH was found to be twice as greater in women (HR_{crude} 2.16, 95% CI 1.36-3.44) than men (HR_{crude} 1.61, 95% CI 0.79-3.30 when there was a family history of stroke in univariable analysis.[94]

Genetic risk factors

Six studies based on genetic variations or polymorphisms as a risk factor for aSAH were included. See **Table 3-17**. NOS3 27-bp-VNTR b/b genotype was associated with the risk of aSAH and was more prevalent in men [164] while clotting factor XIII gene variants increased risk of aSAH in women but not men.[155] Genetic variant rs10757278 on 9p21 also showed an association for the risk of aSAH in women.[160] Equal distribution of ACE gene genotype II was a risk factor for aSAH in both sexes.[163] Likewise, for ADAMST13 gene, no sex specific association was observed.[148] GpIIIa A1/A2 polymorphism neither was a risk factor in Polish population, nor was any sex difference detected.[141]

Other risk factors

There were some other risk factors examined for their association with the risk of aSAH. See **Table 3-18**. Many important risk factors like age, low body mass index (BMI), use of drugs like cocaine and aspirin were mentioned in the several studies but could not be included because of the absence of sex specific analysis. In one study, stress was compared between the sexes by categorizing it into children related stress in women and work related stress in men but these were not significant risk factors for aSAH.[146] Increasing age was a risk factor in a cohort study in both sexes[94] and was associated with decreased risk of aSAH in age groups 35-45 years, 45-55 years and 55-65 years respectively with relative lifetime risk more in women compared to men.[165] In a study, authors reported cold temperature as a risk factor for aSAH in women but not men.[153] High alanine aminotransferase (ALT) levels were associated with risk of aSAH in men but not in women.[149] High aspartate aminotransferase (AST) levels were associated with reduced risk in men while no association with risk was reported in women.[149] Liver disease and urea nitrogen had no association for the risk of aSAH in either sex.[149]

Table 3-8 Studies of the association between female sex and aSAH

Author	Crude risk OR/RR/HR (95% CI)	Adjusted risk OR/RR/HR (95% CI)	Covariates
Female sex **Reference: Male sex**			
Adamski et al[141]	NR	OR 1.95 (1.308-2.907)	Hypertension, High cholesterol, obesity, smoking
Can et al[144]	OR 0.64 (0.55-0.74)	OR 0.69 (0.59–0.80)	Race, hypertension, current & former smoking, younger age, diabetes
Jimenez-Yepes & London˜oFerna´ndez[151]	NR	OR 1.51 (0.88-2.56)	Age, hypertension, cage index, family history, coffee, BMI, fagerstrom index
Kowalski & Nyquist[153]	NR	OR 2.134 (1.801-2.549)	Race, hypertension, maximum daily temperature <70°f, higher maximum & minimum daily relative humidity
Ruiz-Sandoval et al[162]	NR	OR 0.876 (0.570-1.346)	Age, hypertension, diabetes mellitus, alcoholism, current &former smokers
Staalso et al[164]	OR 2.3 (1.7-3.1)	NR	N/A
You et al[166]	OR 1.426 (0.855-2.379)	NR	N/A
Sandvei et al (2009)[168] *	NR	HR 1.9 (1.3-2.7)	Sex, age, smoking, alcohol
Sandvei et al (2011)[169] *	HR 1.7 (CI; NR)	HR 1.9 (1.3-2.7)	Age in 10-year categories (30, 30-39, . . ., 60–69,70 years)

OR; Odds ratio, RR; Relative Risk, HR: Hazard Ratio
*Cohort study

Table 3-9 Studies for female specific risk factors

Author	Risk Factor description	Crude risk OR/RR/HR (95% CI)	Adjusted Risk OR/RR/HR (95% CI)	Covariates
Age at Menarche				
Okamoto et al (2001)[157]	< 13 y	NR	OR 3.24 (1.25–4.03)	Age, hypertension, smoking habits, educational level
	Reference age: ≥ 13 years			
Lindekleiv[94] *	<12 years	HR 1.15 (0.52–2.55)	NR	
	Reference age: 12-14 years			
	>14 years	HR 1.19 (0.69–2.06)	NR	
Menstrual Cycle Regularity				
Okamoto et al (2001)[157]	Reference group: Regular cycle			Age, hypertension, smoking habits, educational level
	Irregular cycle	NR	OR 0.84 (0.48–1.48)	
Age at first pregnancy				
Okamoto et al (2001)[157]	Reference age: <26 years			Age, hypertension, smoking habits, educational level
	≥ 26 years	NR	OR 1.78 (1.13–2.80)	
Age at first childbirth				
Okamoto et al (2001)[157]	Reference age: <26 years			Age, hypertension, smoking habits, educational level
	≥ 26 years	NR	OR 1.45 (0.91–2.33)	

Gravidity

Okamoto et al (2001)[157]	Nulligravidity Reference: ≥ 1 Gravida	NR	OR 4.23 (1.05–7.56)	Age, hypertension, smoking habits, educational level

Contraceptive use

Pettiti & Wingerd[161]	Current Oral Contraception	RR 6.5 (1.9-22.6)	NR	N/A
	Past Oral Contraception	RR 5.3 (1.3-22.0)	NR	
	Current Oral Contraception use & Smoking	RR 21.9 (8.5-56.2)	NR	
	Current Oral Contraception use matched for smoking	RR 6.5 (1.9-22.2)	NR	

Parity

Gaist et al [147] (Patients with codes for surgery of aneurysm)	Reference: Parity1			Index date, age at index date, length of follow-up, smoking
	Parity 2	NR	OR 0.87 (0.64–1.19)	
	Parity 3	NR	OR 0.72 (0.49–1.07)	
	Parity 4	NR	OR 0.71 (0.35–1.45)	
	Parity ≥5	NR	OR 0.25 (0.03–1.89)	
Okamoto et al (2001)[157]	Nulliparity Reference: Parity ≥1	NR	OR 1.82 (0.76–17.5)	Age, hypertension, smoking habits, educational level

Lindekleiv et al[94] *	Nulliparity	HR 0.72 (0.34–1.52)	NR	
	Reference: 1-3			
	>3	HR 1.21 (0.68–2.14)	NR	

Menopausal status

Okamoto et al (2001)[157]	Premenopause	NR	OR 0.67 (0.36–1.23)	Age, hypertension, smoking habits, educational level
	Reference: Postmenopause			
Lindekleiv et al[94] *	Reference: Premenopause			
	Postmenopause	HR 1.38 (0.87–2.19)	NR	

Hormone Replacement Therapy

Lindekleiv et al[94] *	Reference: Never used			N/A
	Current user	HR 0.86 (0.34–2.14)	NR	

Marital status

Lindegard et al[167]*	Reference: All women			N/A
	widows/spinsters	RR 0.63	NR	
	Married	RR 0.98	NR	
	Divorced	RR 1.89	NR	

Migraine history

Petitti & Wingerd[161]	Migraine history	RR 0.6 (0.1-3.2)	NR	N/A

aSAH predilection area

Lindegard et al[167] *	Reference: All women			N/A
	aSAH predilection area	RR 1.81	NR	

*Cohort study

Table 3-10 Studies for smoking status

Author	Risk factor description	Crude risk Male PAR OR/RR/HR (95% CI)	Female PAR OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Smoking status						
Anderson et al[142]	Reference: Never smoker no ETS					Hypertension, diabetes mellitus, alcohol use, BMI, ethnicity
	Current smoking cig/day (1/day at least)	NR	NR	OR 4.0 (1.8–9.2)	OR 7.7 (3.7-15.8)	
	Cig < or eq. to 20 Light	NR	NR	OR 3.5 (1.3-9.4)	OR 5.8 (2.7-12.4)	
	Cig >20 Heavy		NR	OR 7.5 (2.6-21.0)	OR 12.9 (4.2-39.5)	
	Past smoker	NR	NR	OR 0.6 (0.3-1.4)	OR 1.7 (0.8-3.5)	
	Years quit 1-4	NR	NR	OR 0.9 (0.2-4.9)	OR 3.2 (0.9-11.6)	
	Years quit 5-15	NR	NR	OR 0.7 (0.2-2.4)	OR 2.1 (0.7-5.8)	
	Years quit >15	NR	NR	OR 0.4 (0.1-1.2)	OR 1.9 (0.7-5.3)	
	Non-smoker exposed to ETS	NR	NR	OR 0.6 (0.2-1.7)	OR 1.2 (0.6-2.4)	
Bell & Symon[143]	Reference: Lifelong non-smokers					N/A
	Continuing Smokers	RR 3.9 (1.3-12.0)	RR 3.7 (2.3-5.9)	NR	NR	
Canhao et al[145]	Reference: Non-smokers					N/A
	Tobacco Consumption	OR 7.03 (2.65-18.61)	OR 2.48 (0.90-6.83)	NR	NR	

Study	Category	Col1	Col2	Col3	Col4	Adjustment
Gaist et al[147]	Reference: Non-smokers					Index date, age at index date, length of follow-up, parity
	1-9 cig.	N/A	NR	N/A	OR 2.27 (1.62–3.19)	
	>10 cig.	N/A	NR	N/A	OR 3.63 (2.54–5.18)	
Inagawa[149] (2005)	Reference: Non-smokers					Hypertension, heart disease, liver disease, daily drinker, high cholesterol, diabetes mellitus, AST, ALT, UN
	Ever smoker	NR	NR	OR 2.84 (1.39-5.82)	OR 0.59 (0.17-2.02)	
Inagawa[150] (2010)	Reference: Non-smokers					Hypertension, heart disease, daily drinker, high cholesterol, diabetes mellitus
	Ever smoker	NR	NR	OR 4.54 (2.87-7.21)	OR 2.77 (1.52-5.04)	
Juvela et al[152]	Reference: Non-smokers					Hypertension, age, alcohol consumption within 24 hours before onset
	Former smoker	RR 1.64 (0.66-4.06)	RR 0.49 (0.17-1.42)	RR 1.57 (0.61-4.01)	RR 0.49 (0.16-1.49)	
	Current smoker ≤ 10 cig/day	RR 1.42 (0.48-4.14)	RR 1.06 (0.48-2.32)	RR 1.06 (0.34-3.25)	RR 1.17 (0.51-2.72)	
	Current smoker 11-20 cig/day	RR 2.52 (1.03-6.17)	RR 2.75 (1.10-6.88)	RR 2.15 (0.84-5.50)	RR 3.57 (1.33-9.58)	
	Current smoker >20 cig/day	RR 9.59 (5.07-18.15)	RR 3.10 (1.62-5.92)	RR 7.33 (3.76-14.29)	RR 1.98 (0.95-4.14)	
Koshy et al[95]	Reference: Non-smoker					Hypertension, age, diabetes mellitus
	Current smoker	OR 6.33 (3.17-12.62)	N/A	OR 6.08 (3.02-12.22)	N/A	
	Reference: Non-smoker					N/A
	Current smoker	RR 2.2 (1.7-3.0)	RR 2.2 (1.7-2.8)	NR	NR	
	Ever smoker	RR 1.4 (0.9-2.1)	RR 2.7 (1.8-4.1)	NR	NR	
	Current smoking	PAR 23.6%	PAR 2.2%	NR	NR	N/A

	Ever smoking	PAR 10.2%	PAR 3.5%	NR	NR	
Kubota et al[154]	Reference: Non-smoker					N/A
	Smoker	OR 4.40 (1.94-9.98)	OR 1.97 (0.87-4.48)	NR	NR	
Morris et al[156]	Reference: Non-smoker					N/A
	Smoker	RR 2.12 (1.27-3.54)	RR 1.93 (1.43-2.61)	NR	NR	
Okamoto et al (2005)[159]	Reference: Non-smoker					Hypertension, family history for SAH, diabetes mellitus, alcohol consumption
	Current smokers	OR 1.2 (0.7–2.3)	OR 5.7 (2.8–11.6)	OR 1.1 (0.4–2.5)	OR 5.7 (1.5–15.9)	
	Reference: Non-smoker and normotensive					
	Current smoker and normotensive	OR 0.9 (0.4–2.0)	OR 3.9 (1.5–9.7)	OR 1.1 (0.4–2.8)	OR 2.9 (1.1–7.7)	
	Current smoker and hypertensive	OR 8.4 (2.4–29.3)	OR 24.6 (6.7–23.5)	OR 6.9 (1.8–26.6)	OR 23.2 (4.7–45.2)	
	Smoking	PAR 22%	PAR 36%			N/A
Petitti & Wingerd[161]	Reference: Non-smokers					N/A
	Smokers	N/A	RR 5.7 (1.8-17.8)	NR	NR	
	Current oral contraception use and smoking	N/A	RR 21.9 (8.5-56.2)	NR	NR	
	Current oral contraception use matched for smoking	N/A	RR 6.5 (1.9-22.2)	NR	NR	
Lindekleiv et al[94] *	Reference: Never smokers					N/A

Former smoker	HR 0.99 (0.37–2.66)	HR 1.81 (0.79–4.13)	NR	NR
Current daily smoker	HR 3.47 (1.62–7.41)	HR 6.50 (3.56–11.89)	NR	NR

PAR; Population Attributable Risk, ETS; Environmental Tobacco Smoke, ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, BMI; Body mass index, UN; Urea Nitrogen
*Cohort study

Table 3-11 Studies for alcohol consumption

Author	Risk factor description	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Alcohol consumption						
Inagawa (2005)[149]	Reference: Non-drinker					Current regular & former smoking, hypertension, heart disease, liver disease, High cholesterol, diabetes mellitus, AST level, ALT level, UN level
	Daily/occasional drinker	NR	NR	OR 1.52 (0.66-3.49)	OR 0.95 (0.28-3.21)	
Inagawa (2010)[150]	Reference: Non-drinker					Current regular & former smoking, hypertension, heart disease, High cholesterol, diabetes mellitus
	Daily/occasional drinker	NR	NR	OR 1.50 (1.00-2.26)	OR 0.80 (0.43-1.50)	
Juvela et al[152]	Reference: No alcohol intake ≤24 hrs					Age, smoking status, hypertension
	1 to 40 gm ≤24 hrs	RR 0.38 (0.17-0.83)	RR 0.44 (0.20-0.95)	RR 0.34 (0.14-0.81)	RR 0.35 (0.16-.80)	
	41 to 120 gm ≤24 hrs	RR 2.65 (1.28-5.49)	RR 8.16 (3.06-21.78)	RR 2.45 (1.10-5.47)	RR 6.36 (2.26-17.92)	
	> 120 gm ≤24 hrs	RR 7.99 (2.97-21.53)	NR	RR 4.45 (1.54-12.87)	NR	
	Reference: No alcohol intake ≤ 1 week					
	1-150gm ≤ 1 week	RR 1.01 (0.58-1.75)	RR 0.83 (0.50-1.38)	NR	NR	
	150-300 gm ≤ 1 week	RR 3.43 (1.6-7.37)	RR 3.15 (1.07-9.30)	NR	NR	
Koshy et al[95]	Reference: Non-drinkers					N/A
	Daily drinker	RR 2.2 (1.5-3.2)	RR 4.0 (0.8-19.1)	NR	NR	

Kubota et al[154]	Reference: Abstainers					N/A
	Drinker	OR 2.62 (1.23-5.57)	OR 1.90 (0.63-6.85)	NR	NR	
Lindekleiv et al[94]*	Abstainers	HR 0.25 (0.03-2.03)	HR 1.17 (0.61-2.23)	NR	NR	N/A
	Reference: Drinks <1 time per month					
	Drinks 1–4 times per month	HR 1.19 (0.51-2.8)	HR 1.01 (.59-1.74)	NR	NR	
	Drinks >4 times per month	HR 1.25 (0.47-3.67)	HR 1.33 (0.59-2.98)	NR	NR	

ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen
*Cohort study

Table 3-12 Studies for hypertension

Author	Crude risk Male PAR OR/RR/HR/PAR (95% CI)	Female PAR OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Hypertension **Reference: No Hypertension**					
Canhao et al[145]	OR (self-estimated) 4.12 (1.82-9.33)	OR (self-estimated) 7.67 (4.08-14.39)	NR	NR	N/A
Inagawa (2005)[149]			OR 3.20 (1.51-6.79)	OR 4.86 (2.51-9.42)	Current regular & former smoking, heart disease, liver disease, daily drinker, High cholesterol, diabetes mellitus, AST level, ALT level, UN level
Inagawa (2010)[150]			OR 2.75 (1.80-4.21)	OR 3.48 (2.59-4.67)	Current regular & former smoking, heart disease, daily drinker, High cholesterol, diabetes mellitus
Juvela et al[152]	RR 1.75 (1-3.08)	RR 1.68 (0.96-2.94)	NR	NR	N/A
Koshy et al[95]	OR 3.74 (1.64-8.50)	OR 2.57 (1.23-5.37)	OR 4.30 (1.81-10.2)	3.28 (1.40-7.68)	Males: Age, diabetes mellitus, smoking Females: Age, diabetes mellitus
Okamoto et al (2005)[159]	OR 5.4 (2.0–15.0)	OR 4.4 (2.4–8.0)	OR 4.4 (1.3–12.8)	OR 3.7 (1.9–7.2)	Current smoking, family history for SAH, diabetes mellitus, alcohol drinking
	PAR 37%	PAR 37%	N/A	N/A	N/A
Petitti & Wingerd[161]	N/A	RR 1.9 (0.5-6.8)	N/A	NR	N/A
Lindekleiv et al[94]*	HR 2.47 (1.30–4.67)	HR 2.41 (1.55-3.77)	NR	NR	N/A
Systolic Blood pressure (per 10mmHg increase)					
Lindekleiv et al[94]*	HR 1.23 (1.08–1.42)	HR 1.16 (1.06–1.26)	NR	NR	N/A

PAR; Population Attributable Risk, ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen
*Cohort study

Table 3-13 Studies for diabetes mellitus

Author	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Diabetes Mellitus Reference: No Diabetes Mellitus					
Canhao et al[145]	OR (self-estimated) 1.00 (0.26-3.73)	OR (self-estimated) 12.39 (1.56-98.15)	NR	NR	N/A
Inagawa (2005)[149]	NR	NR	OR 0.72 (0.14-3.76)	OR 0.17 (0.05-0.62)	Current regular & former smoking, hypertension, heart disease, liver disease, daily drinker, High cholesterol, AST level, ALT level, UN level
Inagawa (2010)[150]	NR	NR	OR 0.55 (0.30-1.03)	OR 0.26 (0.13-0.53)	Current regular & former smoking, hypertension, heart disease, daily drinker, High cholesterol

ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen

Table 3-14 Studies for coronary artery disease

Author	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Coronary Artery Disease Reference: No Coronary Artery Disease					
Inagawa (2005)[149]	NR	NR	OR 0.44 (0.08-2.28)	OR 0.33 (0.12-0.89)	Current regular & former smoking, hypertension, diabetes mellitus, liver disease, daily drinker, High cholesterol, AST level, ALT level, UN level
Inagawa (2010)[150]	NR	NR	OR 0.92 (0.46-1.86)	OR 1.34 (0.87-2.06)	Current regular & former smoking, hypertension, diabetes mellitus, daily drinker, High cholesterol

ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen

Table 3-15 Studies for hypercholesterolemia and hypertriglyceridemia

Author	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Hypercholesterolemia Reference: No Hypercholesterolemia					
Canhao et al[145]	OR (self-estimated) 0.53 (0.18-1.62)	OR (self-estimated) 1.15 (0.55-2.39)	NR	NR	N/A
Inagawa (2005)[149]	NR	NR	OR 2.47 (0.78-7.82)	OR 3.49 (1.46-8.29)	Current regular & former smoking, hypertension, diabetes mellitus, liver disease, daily drinker, heart disease, AST level, ALT level, UN level
Inagawa (2010)[150]	NR	NR	OR 0.89 (0.50-1.60)	OR 0.73 (0.55-0.98)	Current regular & former smoking, hypertension, diabetes mellitus, daily drinker, heart disease
Triglyceride level > 200 mg/dl					
Canhao et al[145]	OR (self-estimated) 0.64 (0.10-4.12)	OR (self-estimated) 1.00 (0.28-3.63)	NR	NR	N/A

ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen

Table 3-16 Studies for family history

Author	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Family History of aSAH Reference: No family history of aSAH					
Okamoto et al (2003)[158]	NR	NR	OR 3.9 (1.1-16)	OR 3.8 (1.5-9.7)	Hypertension, smoking
Family history of stroke Reference: No family history of stroke					
Lindekleiv et al[94]*	HR 1.61 (0.79-3.3)	HR 2.16 (1.36-3.44)	NR	NR	N/A

*Cohort study

Table 3-17 Studies for genetic risk factors

Author	Crude risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Genetic Risk factors					
GpIIIa A1/A2 Polymorphism					
Adamski et al[141]	NR	NR	No sex difference was observed in gene polymorphism	No sex difference was observed in gene polymorphism	Hypertension, diabetes mellitus, smoking, obesity
Genetic variation at ADAMTS13					
Hanson et al[148]	sex stratified analysis did not detect sex specific association (values not provided)				NR
FXIII Variants					
Ladenvall et al[155]					Hypertension, smoking
FXIII variant H2	NR	NR	OR 1.28 (0.59-2.81)	OR 1.58 (1.031-2.43)	
FXIII variant H3	NR	NR	OR 0.75 (0.28-0.57)	OR 1.95 (1.18-3.40)	
SNP Leu34 allele carriers	NR	NR	OR 1.06 (0.49-2.29)	OR 1.59 (1.01-2.5)	
Genetic variation on 9p21					
Olsson et al[160]	NR	NR	OR 1.27 (0.74-2.16)	OR 1.49 (1.07-2.07)	Hypertension, smoking
NOS 3 b/b genotype of intron-4 27bp VNTR polymorphism					
Staalso et al[164]	OR 2.8 (1.5–5.6)	OR 1.1 (0.7–1.6)	OR 2.7 (1.2-6.5)	OR 1 (0.6-1.6)	Age, hypertension, smoking

GenotypeII of the ACE gene polymorphism

Slowik et al[163]	NR	NR	OR 3.56 (1.43-8.86)	OR 3.86 (1.75-8.51)	Age, hypertension, ischaemic heart disease, smoking, excessive alcohol

ACE; Angiotensin converting enzyme, ADAMTS13; A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif, 13, FXIII; Factor XIII, GpIIIa; Glycoprotein IIIa , NOS3; nitric oxide synthase gene, SNP; single nucleotide polymorphism, VNTR; variable number of tandem repeats

Table 3-18 Miscellaneous risk factors

Author	Crude Risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Adjusted Risk Male OR/RR/HR (95% CI)	Female OR/RR/HR (95% CI)	Covariates
Age					
Lindekleiv et al[94] *	HR 1.12 (1.02-1.23)	HR 1.07 (1.01-1.15)	NR	NR	N/A
Stress					
de Wilde et al[146]	NR	NR	OR 0.79 (0.47-1.33) stress at work <12 months	OR 1.00 (0.69-1.45) children related stress<12 months	Age, smoking, hypertension, daily alcohol
	NR	NR	OR 0.62 (0.38-1.00) stress at work >12months	OR 0.81 (0.56-1.15) children related stress>12 months	
AST>40IU/L					
Inagawa (2005)[149]	NR	NR	OR 0.14 (0.04-0.51)	OR 1.14 (0.42-3.10)	Current regular & former smoking, hypertension, heart disease, liver disease, daily drinker, high cholesterol, diabetes mellitus, ALT level, UN level
ALT>35IU/L					
Inagawa (2005)[149]	NR	NR	OR 5.24 (1.41-19.40)	OR 0.31 (0.09-1.02)	Current regular & former smoking, hypertension, heart disease, liver disease, daily drinker, high cholesterol, diabetes mellitus, AST level, UN level
UN>20mg/dl					
Inagawa (2005)[149]	NR	NR	OR 1.70 (0.61-4.75)	OR 0.69 (0.34-1.40)	Current regular & former smoking, hypertension, heart disease, liver disease, daily drinker, high cholesterol, diabetes mellitus, ALT level, AST level
Liver disease					

Inagawa (2005)[149]	NR	NR	OR 0.81 (0.26-2.52)	OR 2.91 (0.58-12.50)	Current regular & former smoking, hypertension, heart disease & daily drinker, high cholesterol, diabetes mellitus, ALT level, AST level & UN level

ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, UN; Urea Nitrogen

Table 3-19 Measurement or assessment of risk factors in the included studies

Study	Risk factor	Measurement methods
Adamski et al[141]	A1/A2 genotyping for the GpIIIa gene polymorphism	PCR & RFLP
Anderson et al[142]	Smoking	Structured in person interview with standardised questionnaire & medical records
Bell & Symon[143]	Smoking	Self-report
Canhao et al[145]	Smoking	Self-report
	Hypertension	Objective measurement SBP>160mmHg or DBP >95mmHg or antihypertensive medication
	DM	Fasting glucose > 140mg/dl or random glucose assay >200mg/dl
	Hypercholesterolemia	Measurement of fasting cholesterol level
	Hypertriglyceridemia	Measurement of fasting triglyceride level
de Wilde et al[146]	Stress	Marriage and Stressful Life Events Measures (MSLEM) Questionnaire
Gaist et al[147]	Smoking	Self-report
	Parity	Birth and cause of death register
Hanson et al[148]	Variation in ADAMTS13	Genotyping
Inagawa et al (2005)[149]	Smoking	Medical records (Self-report probably)
	Hypertension	Medical history
	DM	Medical history
	Liver disease	Medical history
	Alcohol consumption	Medical records (Self-report probably)
	Heart disease	Medical history
	Serum cholesterol	Blood serum levels
	AST	Blood serum levels
	ALT	Blood serum levels
	UN	Blood serum levels
Inagawa et al (2010)[150]	Smoking	Medical records (Self-report probably)
	Hypertension	Medical history
	DM	Medical history
	Alcohol consumption	Medical records (Self-report probably)
	Heart disease	Medical history
	Serum cholesterol	Blood serum levels
Juvela et al[152]	Smoking	Structured in person interview with questionnaire
	Hypertension	Objective measurement/use of medication
	Alcohol consumption	In person interview with structured in person interview with questionnaire
Koshy et al[95]	Smoking	In person interview with structured questionnaire
	Alcohol consumption	In person interview with structured questionnaire
Kubota et al[154]	Smoking	In person/proxy interview with structured questionnaire
	Alcohol	In person/proxy interview with structured questionnaire
Ladenvall[155]	Polymorphism in FXIII	Genotyping
Lindegard[167]	Marital status	Record linkage
Lindekleiv[94]	Smoking	Self-report
	Hypertension & Systolic blood pressure	Objective measurement (mean of 2nd and 3rd recording SBP> 140mmHg)/Use of medication
	Alcohol consumption	Self-report
	Family history	Self-report

	Menopause status	Self-report
	HRT use	Self-report
	Parity	Self-report
	Age at menarche	Self-report
Morris et al[156]	Smoking	Hospital records
Okamoto et al (2001)[157]	Age at menarche	In person interview with structured questionnaire
	Age at first pregnancy	In person interview with structured questionnaire
	Age at first birth	In person interview with structured questionnaire
	Menopause status	In person interview with structured questionnaire
	Gravidity	In person interview with structured questionnaire
	Parity	In person interview with structured questionnaire
Okamoto et al (2003)[158]	Family history	In person interview with structured questionnaire
Okamoto et al (2005)[159]	Smoking	In person interview with structured questionnaire
	Hypertension	In person interview with structured questionnaire (previous diagnosis)
Olsson et al[160]	Variation on 9p21 chromosome	Genotyping
Petitti & Wingerd[161]	Smoking	Self-report
	Hypertension	Self-report
	Contraceptive use	Self-report
	Migraine history	Self-report
Slowik et al[163]	ACE I/D polymorphism	PCR
Staalso et al[164]	NOS3 polymorphism	Genotyping
Vlak et al[165]	Hypertension	In person interview with structured questionnaire & medical records
	Smoking	In person interview with structured questionnaire
	Hypercholesterolemia	In person interview with structured questionnaire & medical records
	Family history	In person interview with structured questionnaire & medical records

ACE I/D; Angiotensin converting enzyme insertion/deletion, ADAMTS13; A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif, 13, ALT; Alkaline aminotransferase, AST; Aspartate aminotransferase, DBP; diastolic blood pressure, DM; Diabetes mellitus, FXIII; Factor XIII, GpIIIa; Glycoprotein IIIa, HRT; Hormone replacement therapy, NOS3; Nitric oxide synthase gene, PCR; Polymerase chain reaction, RFLP; Restriction Fragment Length Polymorphism, SBP; systolic blood pressure, SNP; single nucleotide polymorphism, UN; Urea Nitrogen, VNTR; variable number of tandem repeats

A

Study	Year	OR (95% CI)	Weight %
Can et al	2017	0.64 (0.55, 0.74)	34.67
Staalso	2014	2.30 (1.70, 3.10)	33.74
You et al	2008	1.43 (0.86, 2.38)	31.59
Overall (I-squared = 96.7%, p = 0.000)		1.27 (0.50, 3.20)	100.00

NOTE: Weights are from random effects analysis

B

Study	Year	OR (95% CI)	Weight %
Adamski	2009	1.95 (1.31, 2.91)	16.88
Can et al	2017	0.69 (0.59, 0.80)	18.25
Jimenez	2008	1.51 (0.88, 2.56)	15.80
Kowalski & Nyquist	2015	2.13 (1.80, 2.55)	18.17
Ruiz Sandoval	2009	0.88 (0.57, 1.35)	16.65
Slowik et al	2004	2.70 (1.12, 4.59)	14.25
Overall (I-squared = 95.3%, p = 0.000)		1.44 (0.83, 2.52)	100.00

NOTE: Weights are from random effects analysis

C

Study	Year	HR (95% CI)	Weight %
Sandvei et al	2009	1.90 (1.30, 2.70)	50.00
Sandvei et al	2012	1.90 (1.30, 2.70)	50.00
Overall (I-squared = 0.0%, p = 1.000)		1.90 (1.47, 2.46)	100.00

NOTE: Weights are from random effects analysis

Figure 3-2 Association between female sex and aSAH

(A) Pooled OR$_{crude}$ for case-control studies (B) Pooled OR$_{adjusted}$ for case-control studies(C) Pooled HR$_{adjusted}$ for cohort studies
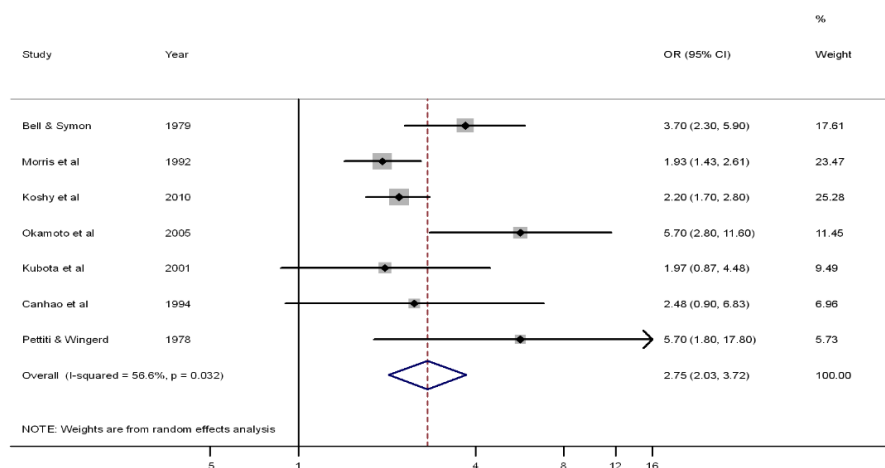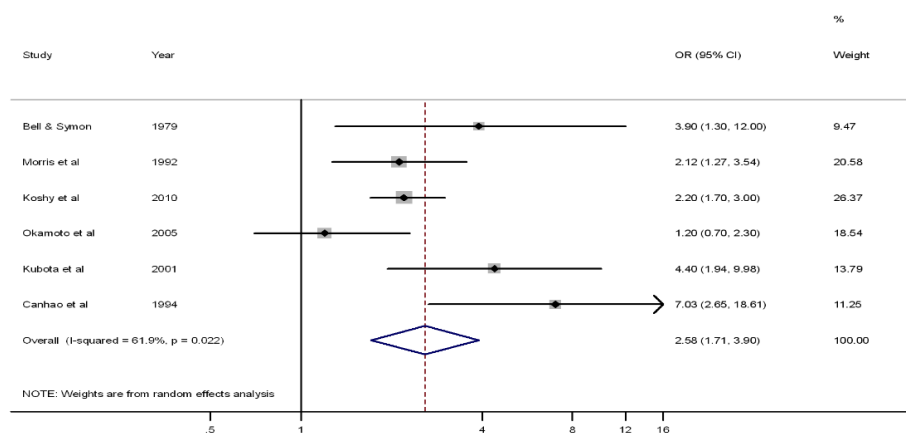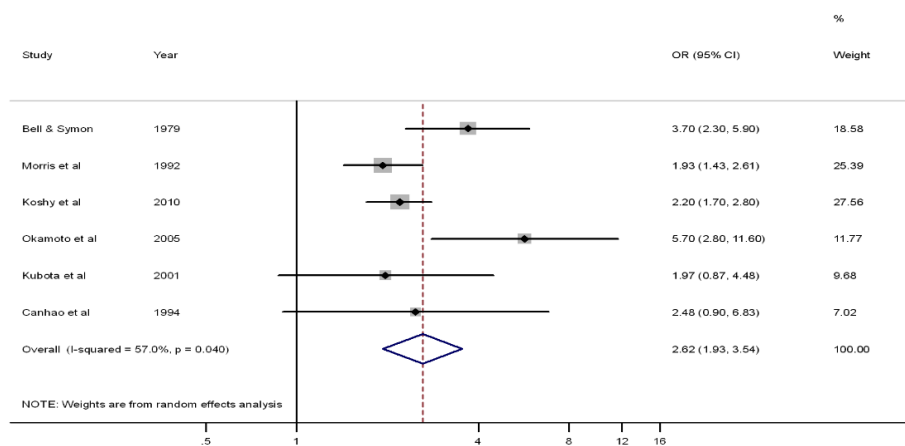
Figure 3-3 Association between smoking and aSAH; Pooled OR_crude (case-control studies)

(A) all women studies (B) subgroup analysis in men (C) subgroup analysis in women
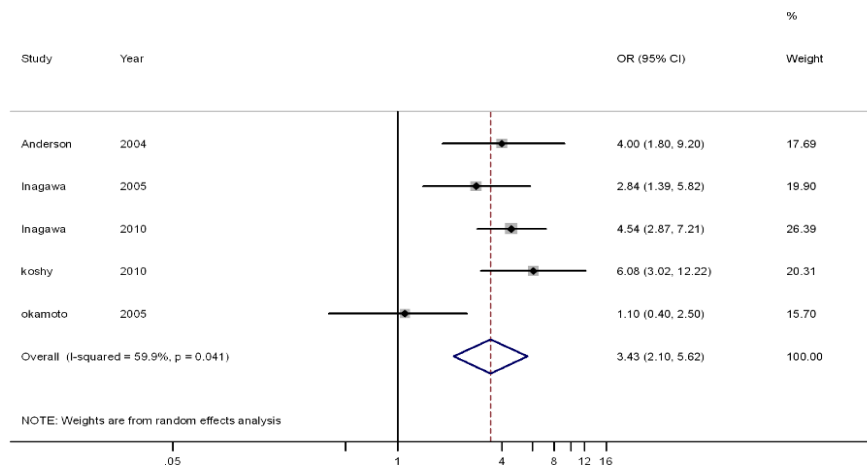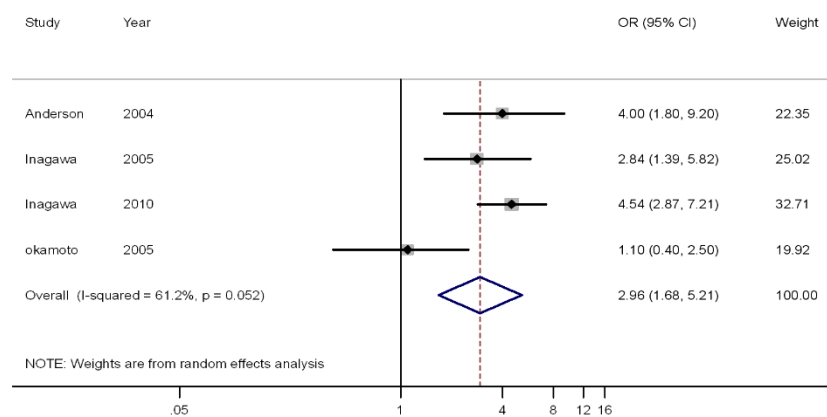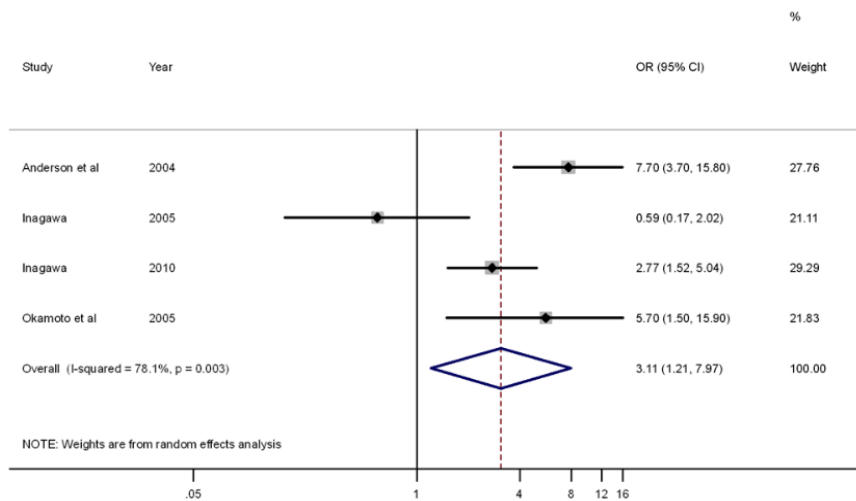
Figure 3-4 Association between smoking and aSAH; Pooled OR$_{adjusted}$ (case-control studies)

(A) all men studies (B) subgroup analysis in men (C) subgroup analysis in women
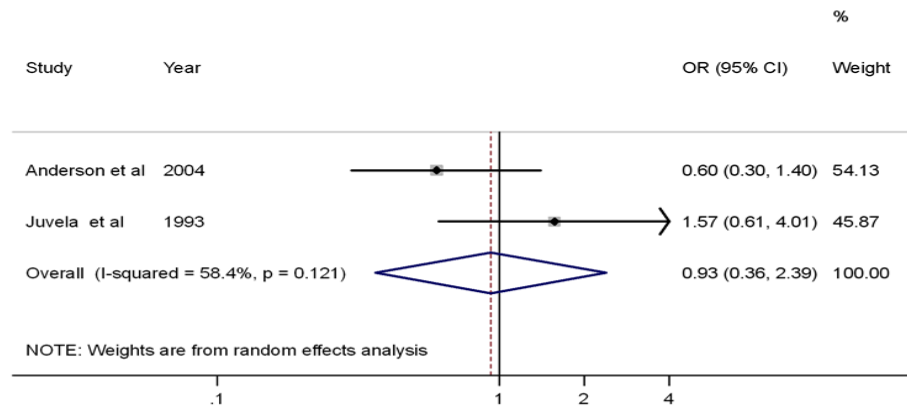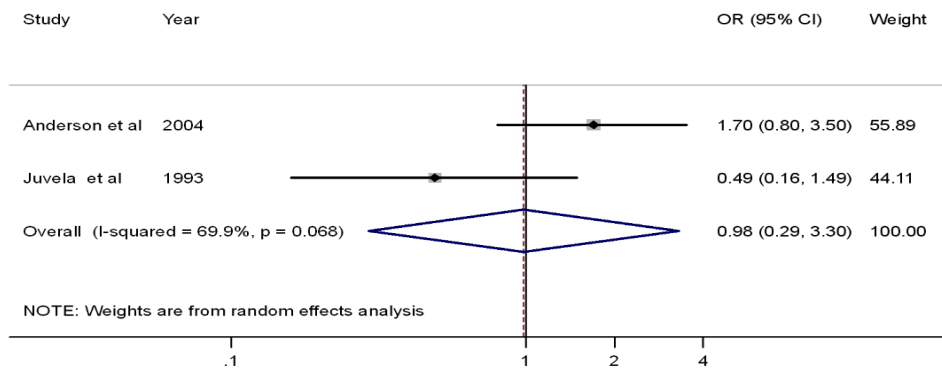
Figure 3-5 Association between former smoking and aSAH; Pooled OR$_{adjusted}$ (case-control studies)

(A) in men (B) in women

A

Study	Year	OR (95% CI)	% Weight
Kubota et al	2001	2.62 (1.23, 5.57)	20.11
Koshy	2010	2.20 (1.50, 3.20)	79.89
Overall (I-squared = 0.0%, p = 0.685)		2.28 (1.62, 3.20)	100.00

NOTE: Weights are from random effects analysis

B

Study	Year	OR (95% CI)	Weight
Kubota et al	2001	1.90 (0.63, 6.85)	63.87
Koshy	2010	4.00 (0.80, 19.10)	36.13
Overall (I-squared = 0.0%, p = 0.462)		2.49 (0.96, 6.45)	100.00

NOTE: Weights are from random effects analysis
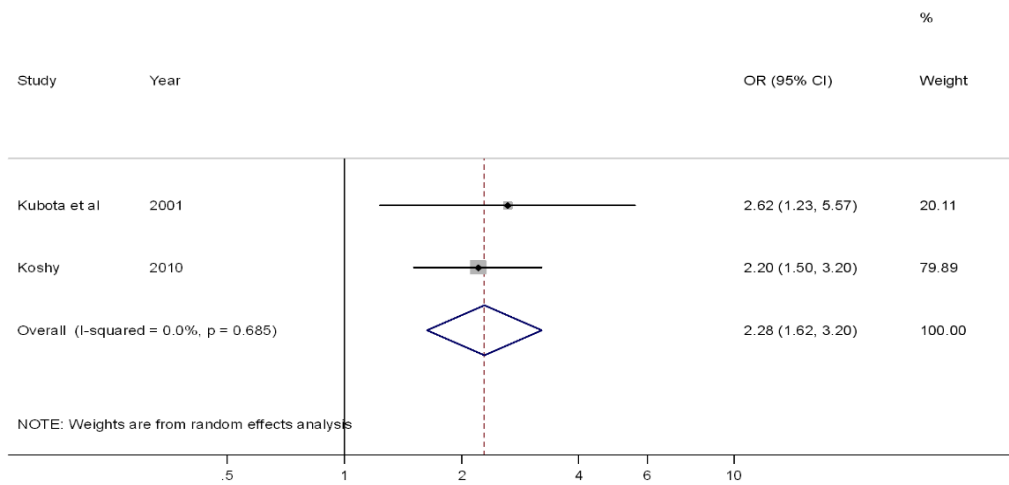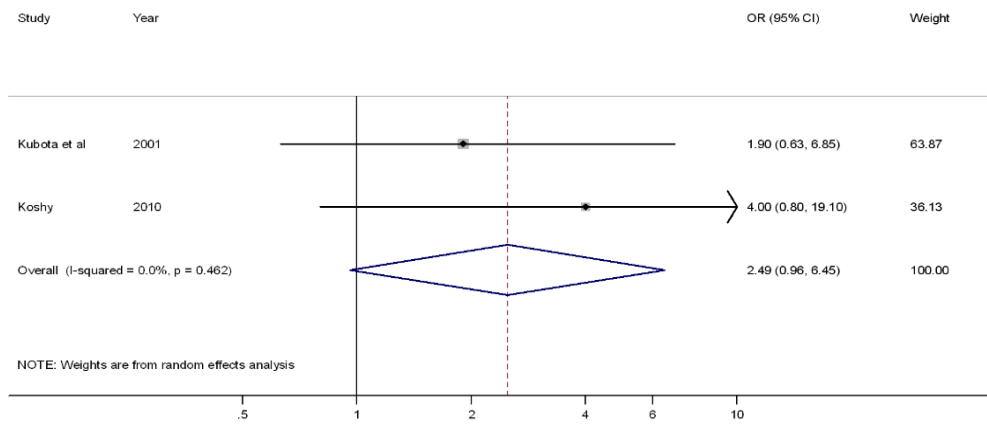
Figure 3-6 Association between alcohol consumption and aSAH; Pooled OR$_{crude}$ (case-control studies)

(A) in men (B) in women

A

Study	Year	OR (95% CI)	% Weight
Inagawa	2005	1.52 (0.66, 3.49)	19.33
Inagawa	2010	1.50 (1.00, 2.26)	80.67
Overall (I-squared = 0.0%, p = 0.978)		1.50 (1.04, 2.17)	100.00

NOTE: Weights are from random effects analysis

B

Study	Year	OR (95% CI)	Weight
Inagawa	2005	0.95 (0.28, 3.21)	20.78
Inagawa	2010	0.80 (0.43, 1.50)	79.22
Overall (I-squared = 0.0%, p = 0.806)		0.83 (0.48, 1.45)	100.00

NOTE: Weights are from random effects analysis
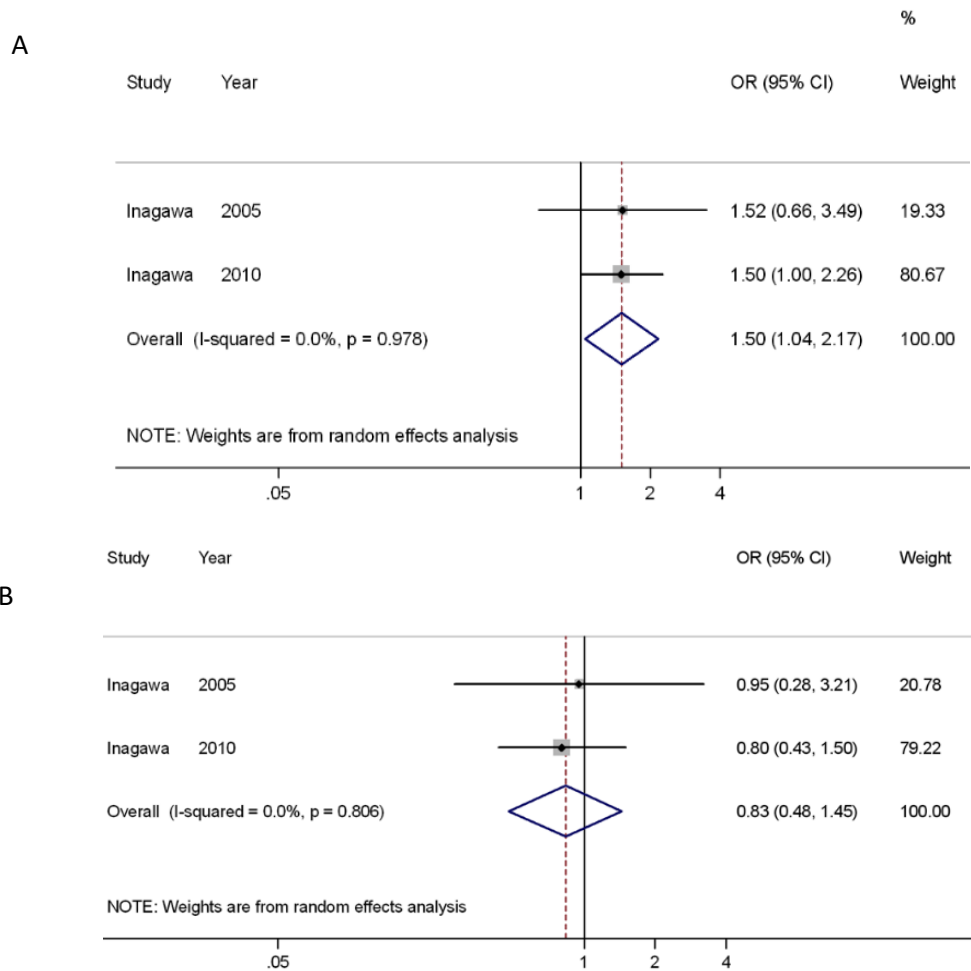
Figure 3-7 Association between alcohol consumption and aSAH; Pooled OR$_{adjusted}$ (case-control studies)

(A) in men (B) in women
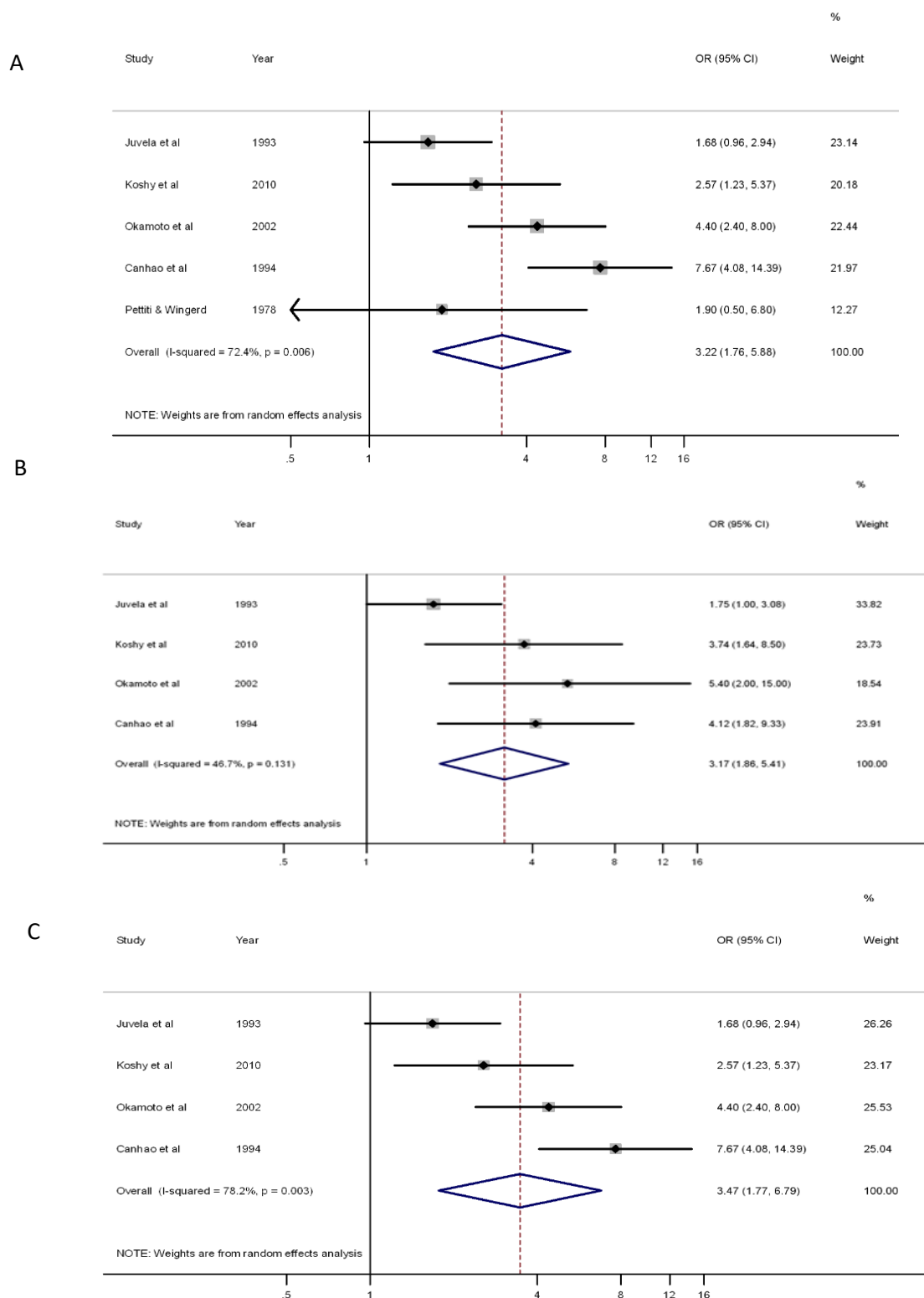
Figure 3-8 Association between hypertension and aSAH; Pooled OR$_{crude}$ (case-control studies)

(A) all women studies (B) subgroup analysis in men (C) subgroup analysis in women
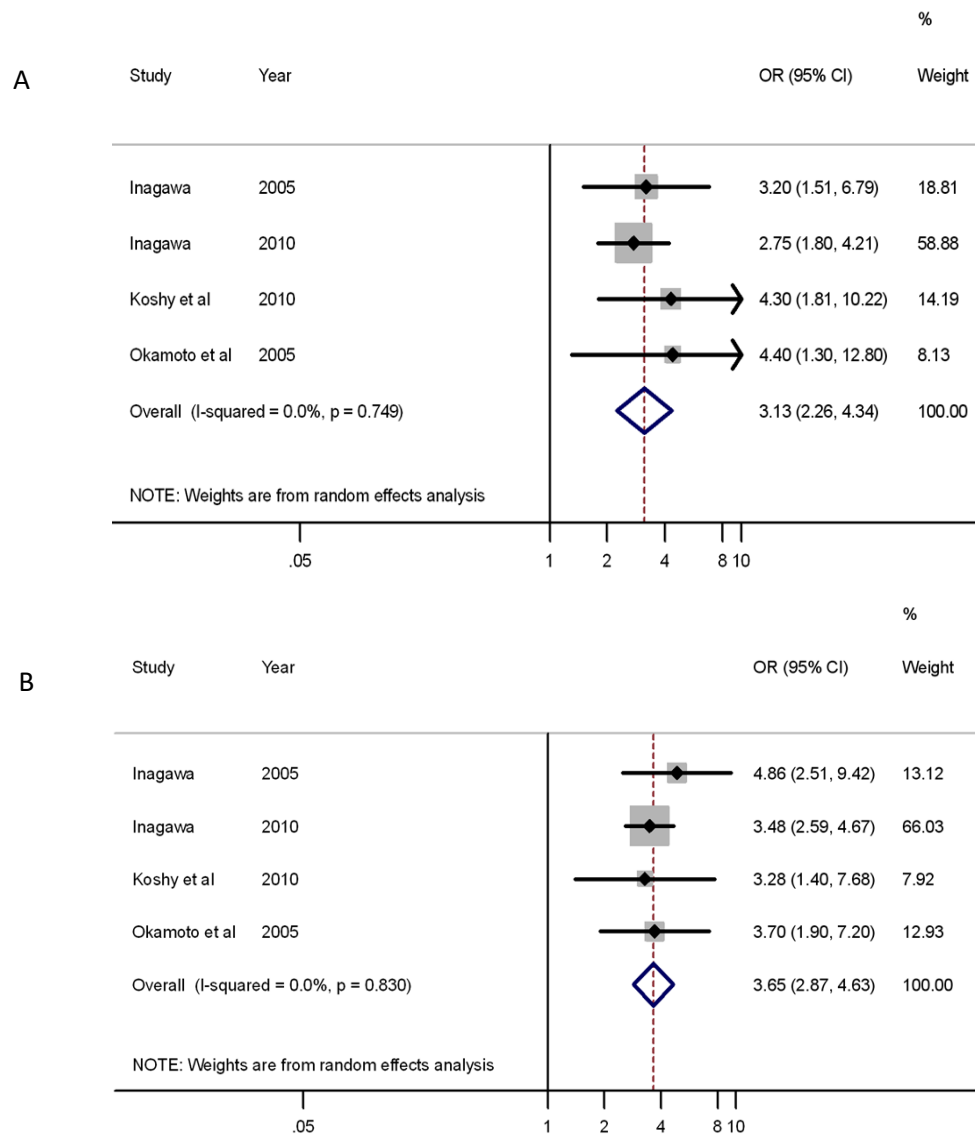
Figure 3-9 Association between hypertension and aSAH; Pooled OR_adjusted (case-control studies)
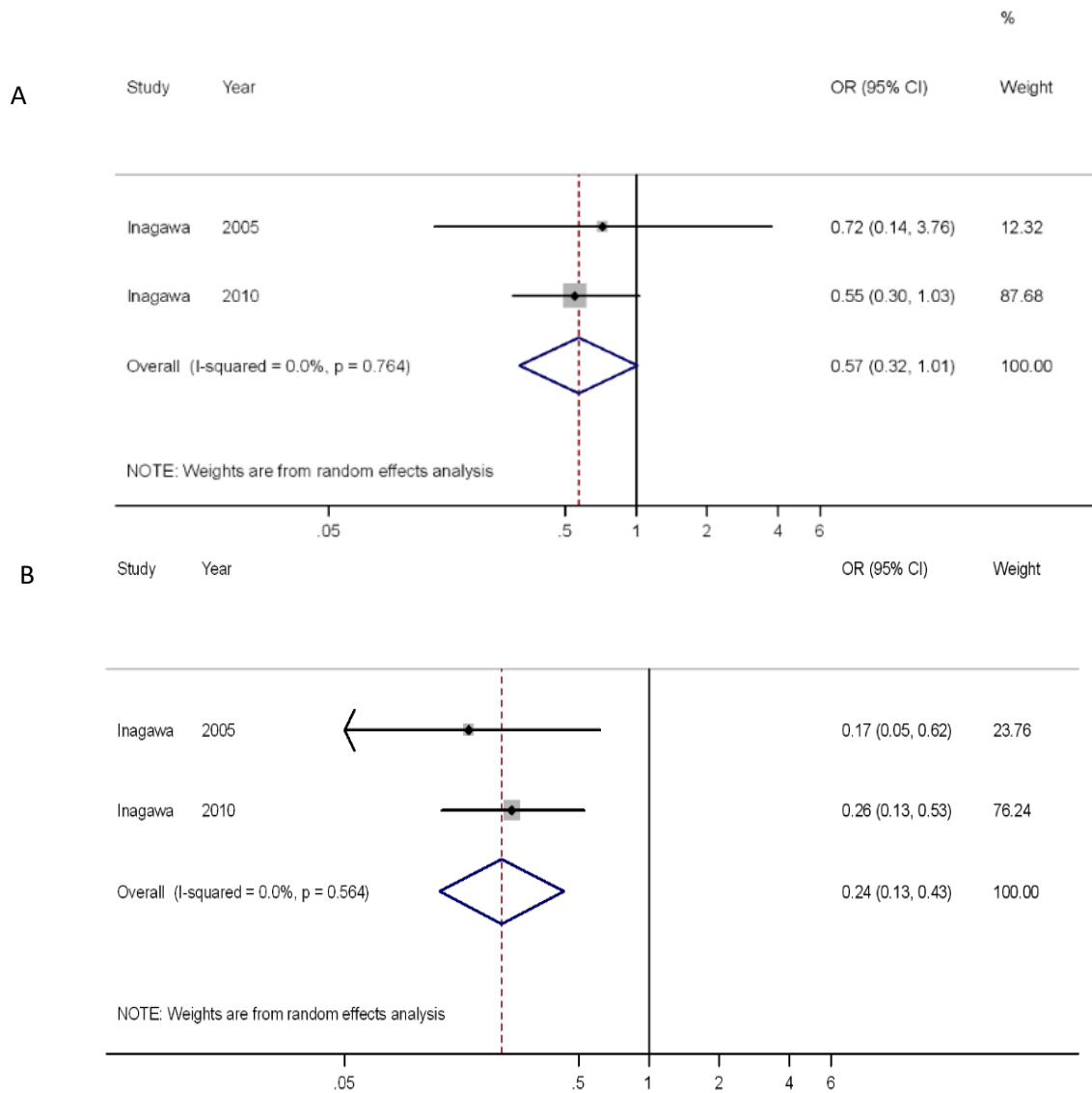
 (A) in men (B) in women

Figure 3-10 Association between diabetes mellitus and aSAH; Pooled OR$_{adjusted}$ (case-control studies)

(A) in men (B) in women

A

Study	Year		OR (95% CI)	% Weight
Inagawa	2010		0.92 (0.46, 1.86)	85.18
Inagawa	2005		0.44 (0.08, 2.28)	14.82
Overall (I-squared = 0.0%, p = 0.426)			0.82 (0.43, 1.57)	100.00

NOTE: Weights are from random effects analysis

B

Study	Year		OR (95% CI)	% Weight
Inagawa	2005		0.33 (0.12, 0.89)	44.58
Inagawa	2010		1.34 (0.87, 2.06)	55.42
Overall (I-squared = 84.2%, p = 0.012)			0.72 (0.18, 2.81)	100.00

NOTE: Weights are from random effects analysis
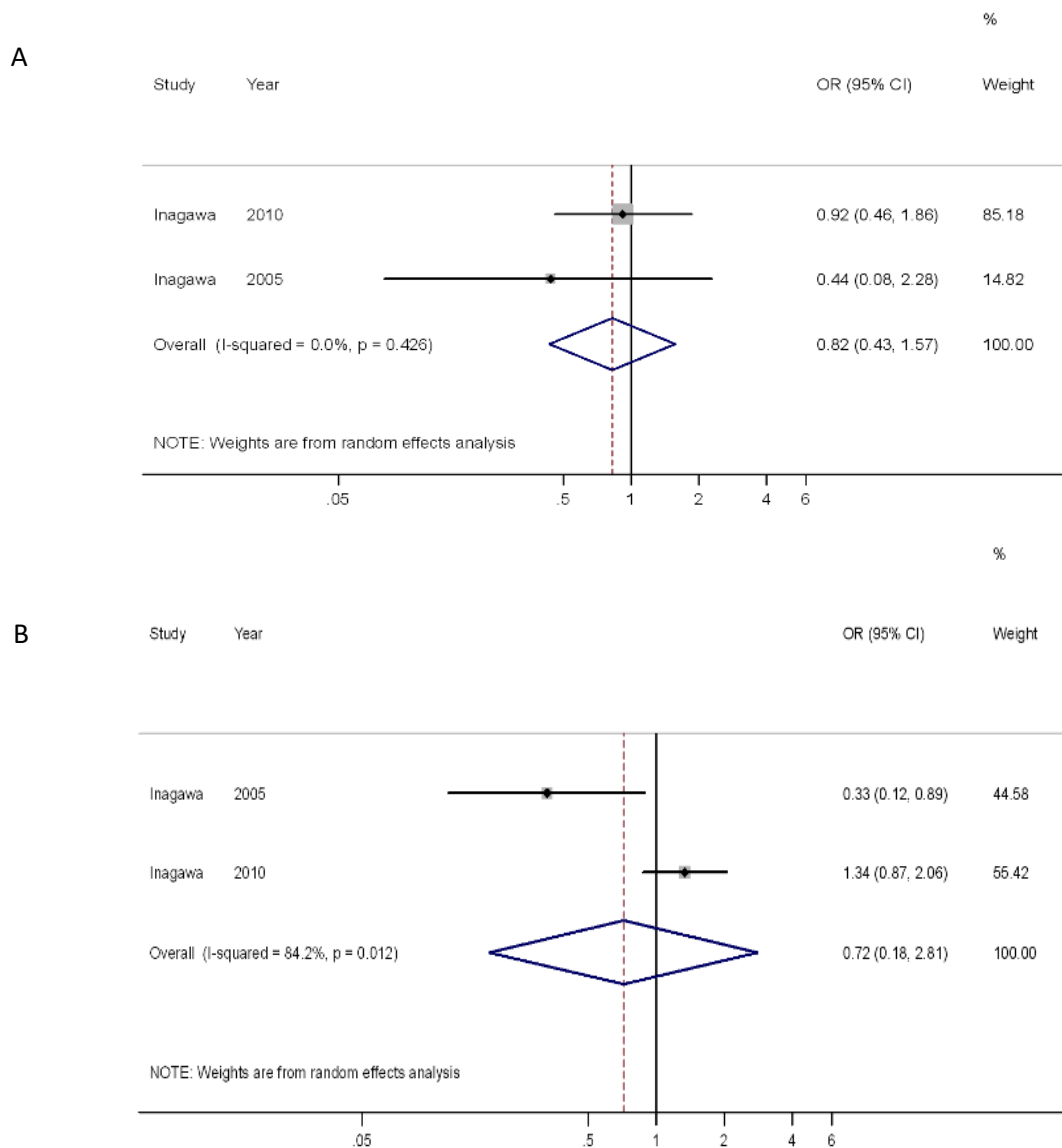
Figure 3-11 Association between coronary artery disease and aSAH; Pooled OR$_{adjusted}$ (case-control studies)
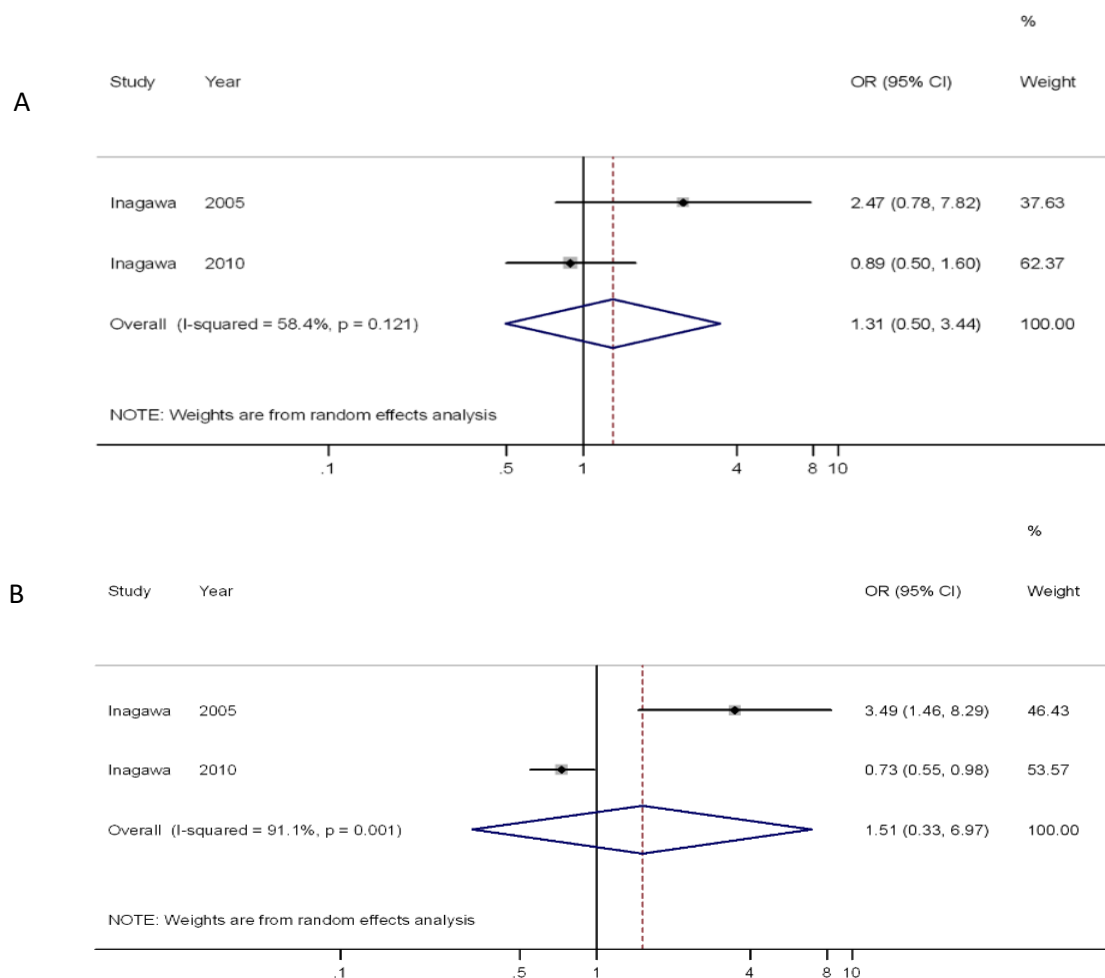
(A) in men (B) in women

Figure 3-12 Association between hypercholesterolemia and aSAH; Pooled OR$_{adjusted}$ (case-control studies)

(A) in men (B) in women

Analysis of Heterogeneity by Regions

We conducted meta-regression for the risk factors when there were 3 or more studies for a risk factor and a region was common for at least 2 studies. The region with high incidence was taken as reference. We could only analyse the difference by region for female sex (adjusted Odds ratio from case-control studies), smoking (adjusted and unadjusted Odds ratio), and hypertension (unadjusted Odds ratio). Regional differences in these risk factors were not statistically significant. See **Table 3-20, Table 3-21, Table 3-22, Table 3-23, Table 3-24, Table 3-25** and **Table 3-26.**

Table 3-20 Analysis of heterogeneity based on region for female sex (unadjusted) as a risk factor

Geographic Region	No. of studies	OR (95% CI)	P-value
Europe	2	Reference	
Latin America	2	0.50(0.07-3.39)	0.33
USA	2	0.53(0.09-3.36	0.36

Table 3-21 Analysis of heterogeneity based on region for smoking (unadjusted) as a risk factor in men

Geographic Region	No. of studies	OR (95% CI)	P-value
Europe	3	Reference	
South East Asia	3	0.61(0.15-2.51)	0.39

Table 3-22 Analysis of heterogeneity based on region for smoking (unadjusted) as a risk factor in women

Geographic Region	No. of studies	OR (95% CI)	P-value
Europe	3	Reference	
South East Asia	3	1..08(0.37-3.16)	0.84

Table 3-23 Analysis of heterogeneity based on region for hypertension (unadjusted) as a risk factor in men

Geographic Region	No. of studies	OR (95% CI)	P-value
Europe	2	Reference	
South East Asia	2	1.77(0.18-16.76)	0.37

Table 3-24 Analysis of heterogeneity based on region for hypertension (unadjusted) as a risk factor in women

Geographic Region	No. of studies	OR (95% CI)	P-value

Europe	2	Reference	
South East Asia	2	0.95(0.02-32.23)	0.96

Table 3-25 Analysis of heterogeneity based on region for smoking (adjusted) as a risk factor in men

Geographic Region	No. of studies	OR (95% CI)	P-value
Western Pacific	1	Reference	
South East Asia	3	0.65(0.01-24.59)	0.66

Table 3-26 Analysis of heterogeneity based on region for smoking (adjusted) as a risk factor in women

Geographic Region	No. of studies	OR (95% CI)	P-value
Western Pacific	1	Reference	
South East Asia	3	0.28(0.001-54.19)	0.41

3.6   Discussion

In this systematic review, risk factors for their sex-specific association with aSAH, were identified. Most risk factors had an equal effect on the risk or odds of aSAH in men and women. A large proportion of studies had to be excluded because there was no sex specific analysis of risk factors.

Female sex was associated with a greater risk of aSAH compared to male sex. This aligns with the findings of several female-only risk factors that are broadly related to greater exposure to reproductive hormones including early age at menarche, later age at pregnancy and nulligravidity. Women suffer from aSAH after menopause which suggests that estrogen might be important in protection against the rupture of aneurysm [170] though it might not be the main factor for aSAH.[171] Estrogen promotes vessel wall strengthening by increasing connective tissue and endothelial NO production, and decreasing TNF-α function which is pro-inflammatory cytokine.[172] The estrogenic change in menopausal women might stimulate aneurysm formation and rupture. The absence of this strong estrogen withdrawal in males could be one factor contributing to the lower incidence in men compared to women. The underlying explanation for this may be the number of menstrual cycles, which is greater in women with early age of menstruation.[170] Estrogen levels change markedly during the menstrual cycle, with a deficiency of estrogen in immediate perimenstrual phase. Estrogen deficiency can lead to changes in vascular haemodynamics and microanatomy increasing its fragility[173], as it is

protective against vessel injury by nitric oxide production, reducing oxidative stress [174] and, decreases TNF-α function which is pro-inflammatory cytokine.[172] Therefore, the greater number of menstrual cycles in women, the greater the exposure to these estrogenic changes. There is a need for greater understanding of the role of hormones in cerebral aneurysm rupture as this may be a therapeutic target to reduce aSAH, particularly in women. This is unlikely to be a simple task given the conflicting effects of currently available therapies on risk of aSAH with oral contraceptives increasing [175] and hormone replacement therapy decreasing [176] the risk.

Risk factors such as smoking, hypertension, increased systolic blood pressure, family history of aSAH and age were associated with a similar increased risk of aSAH in both sexes. Although smoking was equally a risk factor for aSAH in both sexes there was some evidence of a larger risk of aSAH in women, compared to men, who smoked heavily.[172] Cigarette smoking can cause endothelial dysfunction, haemodynamic stress, and promote inflammatory response that affects extracellular matrix leading to the formation of aneurysm and, further breakdown of matrix and cell death causes to aneurysmal rupture.[177] Hypertension increases the risk of aSAH in men and women equally through damaging the endothelium, occluding vessel wall and connective tissue synthesis[172], and affecting the release of mediators like matrix metalloproteinase 13 [178] and nitric oxide (NO).[179] Matrix metalloproteinase 13 breaks down extracellular matrix [178] and nitric oxide (NO) promotes oxidative stress [179], which can cause aneurysm rupture.[172] The role of family history in the occurrence of aSAH in men and women may be due to shared behavioural and genetic factors. Several genetic risk factors equally affected men and women including variation in ADAMTS13 gene[148] and ACE enzyme gene insertion/deletion polymorphism.[163] When endothelial injury occurs, ADAMTS13 protease inhibits thrombus formation and decreases vascular inflammation in response to contents released by platelets.[180] Therefore, variation in ADAMST13 gene is a possible pathophysiological mechanism for aSAH in men and women. Some authors observed that the insertion/deletion (I/D) polymorphism of the (ACE) gene increased the risk of aSAH [163]. This polymorphism is linked with hypertension,[181] a known risk factor for aSAH, and with other cardiovascular diseases such as coronary artery disease[182] and ischaemic stroke.[183] These finding suggest that the management of traditional risk factors for stroke through lifestyle modification and medications should remain the key targets for primary prevention of aSAH, as well as stroke in general.[119]

Some risk factors for aSAH were only present in men. This may be attributable to the dose of the risk factor. For example, the observation that alcohol consumption was more hazardous in

men than women may be attributable to the heavier consumption of alcohol in men.[95, 152, 154] There are several mechanisms linking alcohol consumption to aSAH. High levels of alcohol consumption induce oxidative stress that damages the endothelium which may cause aneurysm formation and rupture.[179] Heavy alcohol consumption can lead to increase in blood pressure,[184] which itself is an independent risk factor for aSAH.[185] In a related finding, higher ALT levels increased the risk of aSAH in men but not women. High ALT levels are usually associated with liver disease or cirrhosis of liver, alcoholism being one of the causes, making a plausible link to aSAH.[186] The mechanisms underlying the greater risk of aSAH in men than women associated with high ALT levels remain unknown.[149] Current primary prevention guidelines for stroke, which include aSAH, counsel against heavy alcohol consumption. This should be a focus of management for men with existing aneurysms.[119] Endothelial NOS gene (NOS3) 27-bp-VNTR b/b genotype polymorphism was also a risk for aSAH in men only.[164] It is unclear why men and not women with this polymorphism may have a greater risk of aSAH. However, as endothelial nitric oxide synthase (NOS) derives NO and is involved in vasodilation and protection from thrombosis, a pathophysiological link to aSAH is reasonable.[187] Increasingly knowledge of genetic risk factors for aneurysm rupture made lead to more individualised approaches to management of people with aneurysms.

Some risk factors were associated with an increased risk of aSAH in women but not in men. Clotting factor XIII gene haplotypes H2 & H3 were associated with the risk of aSAH in women but not men. In the same study, Ladenvall et al reported carriers of FXIII 34Leu allele were also associated with the risk of aSAH more in women than in men.[155] Coagulation factor XIII induces cross-linking of fibrin for strengthening the thrombus and wound healing.[188] The variation in 9p21 (lead SNPrs10757278) was also a risk factor for aSAH in women. The association between 9p21 and cerebral aneurysm, aortic aneurysms, coronary artery disease, and ischaemic stroke has been observed in previous studies.[189-191] The authors of these studies did not explore why these particular factors may increase risk in women but not men. We hypothesise that statistical power may have contributed as these studies tended to include more women (74%) than men. In some studies, there were trends towards an association in men, but these failed to reach significance. Larger samples, potentially through individual participant data analyses, may be required to examine these sex differences in detail. The differences in genetic variations could potentially explain the sex differences in aSAH. With replication of these findings in larger datasets, genetic risks for aSAH hold promise as tools to identify people with aneurysms at high risk of rupture that should undergo securement.

Some risk factors had inverse association with the risk or odds of aSAH in men and women. High levels of AST were associated with a reduced risk of aSAH in men for reasons that are not clear.[149] Diabetes mellitus decreased the risk of aSAH in women but not men, although a similar non-significant trend was noted in men. Others have suggested that people with diabetes might have a greater risk of dying from other causes and thus the chances of SAH occurrence is less.[49] Diabetics have higher BMI which is associated with a lower risk of aSAH[169] for reasons that are not clear. Diabetics may change their lifestyles including through healthier diets and be more likely to take medications for hypertension [192] which might prevent the rupture of the aneurysm. There were some factors that were not found to be associated with risk of aSAH in either sex, including former smoking, coronary artery disease, hypercholesterolemia, hypertriglyceridemia, liver disease and urea nitrogen.

3.6.1 Limitations and Strengths

There were several limitations of our study. Firstly, only published data was used, and therefore, some studies that were unpublished because of negative findings may have been missed. Secondly, many important risk factors were not addressed separately in men and women such as lifestyle factors (e.g. BMI, physical activity), environmental factors (e.g. seasonal fluctuations, pollution), ethnicity, and anatomical location and morphology of aneurysm. Most studies based on risk factors, did not aim to find sex differences in risk factors for aSAH. There were very few studies for each risk factor; therefore, pooled estimates might be underpowered to explore the sources of heterogeneity. All studies showed that aneurysm presence was confirmed through angiographic techniques or during surgery or at autopsy, but we included the studies which mentioned presence of aneurysm in all cases but not the means of how it was confirmed, which was another limitation. The strengths of the study are use of the comprehensive list of risk factors in our search strategy, systematic approach, wide time-period, and inclusion of studies with genetic risk factors.

3.6.2 Conclusion

In conclusion, it was surprising that not many risk factors for aSAH differed between the sexes given the difference in incidence between men and women. Many studies identified could not be included as the data were not reported separately for men and women. There should be efforts to undertake secondary analyses of these existing studies. This will help us to understanding the risk factors for aSAH in men and women and inform prevention efforts. It should be noted that the prevalence of unruptured intracranial aneurysms (UIA) is greater in

women than in men with prevalence ratio of 1.61(1.02-2.54) [193] and earlier identification could alleviate the burden of aSAH incidence in women. The clinical guidelines for UIA do not mention women as a high-risk group; [44] a point to ponder over. We also recommend studies exploring aSAH risk factors linked to hormones, as these may assist prevention and management of aneurysmal rupture in women but also men. In the meantime, the management of known risk factors for aSAH including hypertension, smoking and heavy alcohol consumption, should be the focus of efforts to prevent aSAH in men and women.

Appendix A: Sex differences in Risk factors for Aneurysmal Subarachnoid Haemorrhage: Systematic Review and Meta-analysis

Search strategies

Embase via ovid

1. (sex adj3 characteristic$1).ab,kw,ti.

2. (sex adj3 difference$1).ab,kw,ti.

3. (gender adj3 difference$1).ab,kw,ti.

4. sex difference/

5. sex based.ab,kw,ti.

6. sex distribution.ab,kw,ti.

7. sex factors.ab,kw,ti.

8. sexual dimorphism.ab,kw,ti.

9. female$1.ab,kw,ti.

10. male$1.ab,kw,ti.

11. girl$1.ab,kw,ti.

12. boy$1.ab,kw,ti.

13. (men or man).ab,kw,ti.

14. wom#n.ab,kw,ti.

15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. subarachnoid hemorrhage/

17. subarachnoid hemorrhage.ab,kw,ti.

18. Aneurysmal Sub-arachnoid h?emorrhage.ab,kw,ti.

19. aSAH.ab,kw,ti.

20. ruptured brain aneurysm$1.ab,kw,ti.

21. ruptured cerebral aneurysm$1.ab,kw,ti.

22. ruptured intracranial aneurysm$1.ab,kw,ti.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. risk factor/

25. risk factor$1.ab,kw,ti.

26. smoking/

27. smoking.ab,kw,ti.

28. tobacco use*.ab,kw,ti.

29. hypertension/

30. hypertension.ab,kw,ti.

31. blood pressure/

32. blood pressure.ab,kw,ti.

33. drinking behavior/

34. drinking behavio?r.ab,kw,ti.

35. Alcohol drinking.ab,kw,ti.

36. estrogen/

37. estrogen.ab,kw,ti.

38. oestrogen.ab,kw,ti.

39. cocaine/

40. Cocaine.ab,kw,ti.

41. hypercholesterolemia/

42. Hypercholesterolemia.ab,kw,ti.

43. diabetes mellitus/

44. Diabetes Mellitus.ab,kw,ti.

45. familial stroke.ab,kw,ti.

46. (family history adj5 stroke).ab,kw,ti.

47. hormone substitution/

48. hormone substitution.ab,kw,ti.

49. hormone replacement therapy.ab,kw,ti.

50. menarche/

51. menarche.ab,kw,ti.

52. menopause/

53. menopause.ab,kw,ti.

54. premenopause/

55. premenopause.ab,kw,ti.

56. postmenopause/

57. postmenopause.ab,kw,ti.

58. body mass index/

59. body mass index.ab,kw,ti.

60. Ovariectomy/

61. Ovariectomy.ab,kw,ti.

62. oophorectomy.ab,kw,ti.

63. hysterectomy/

64. Hysterectomy.ab,kw,ti.

65. androgen deprivation therapy/

66. androgen deprivation therapy.ab,kw,ti.

67. breast feeding/

68. breast feeding.ab,kw,ti.

69. erectile dysfunction/

70. Erectile dysfunction.ab,kw,ti.

71. orchiectomy/

72. orchiectomy.ab,kw,ti.

73. antiandrogen/

74. anti androgen.ab,kw,ti.

75. androgen antagonist.ab,kw,ti.

76. Gonadotrophin releasing hormone agonist.ab,kw,ti.

77. testosterone/

78. testosterone.ab,kw,ti.

79. sex hormone binding globulin/

80. sex hormone binding globulin.ab,kw,ti.

81. kidney polycystic disease/

82. autosomal dominant polycystic kidney disease.ab,kw,ti.

83. Marfan syndrome/

84. Marfan syndrome.ab,kw,ti.

85. nicotine/

86. nicotine.ab,kw,ti.

87. caffeine/

88. caffeine.ab,kw,ti.

89. cardiovascular disease/

90. cardiovascular disease.ab,kw,ti.

91. ethnicity/

92. ethnicity.ab,kw,ti.

93. ethnic groups.ab,kw,ti.

94. social status/

95. social status.ab,kw,ti.

96. socioeconomic status.ab,kw,ti.

97. Exercise/

98. exercise.ab,kw,ti.

99. physical activity.ab,kw,ti.

100. sexual behavior/

101. sexual behavio?r.ab,kw,ti.

102. sexual activity.ab,kw,ti.

103. (location adj4 brain aneurysm).ab,kw,ti.

104. (location adj4 cerebral aneurysm).ab,kw,ti.

105. (location adj4 intracranial aneurysm).ab,kw,ti.

106. (shape adj4 brain aneurysm).ab,kw,ti.

107. (shape adj4 cerebral aneurysm).ab,kw,ti.

108. (shape adj4 intracranial aneurysm).ab,kw,ti.

109. (size adj4 brain aneurysm).ab,kw,ti.

110. (size adj4 cerebral aneurysm).ab,kw,ti.

111. (size adj4 intracranial aneurysm).ab,kw,ti.

112. parity/

113. parity.ab,kw,ti.

114. pregnancy/

115. pregnancy.ab,kw,ti.

116. gravidity.ab,kw,ti.

117. age/

118. age.ab,kw,ti.

119. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118

120. 15 and 23 and 119

Medline via ovid

1. (sex adj3 characteristic$1).ab,kf,ti.

2. (sex adj3 difference$1).ab,kf,ti.

3. (gender adj3 difference$1).ab,kf,ti.

4. Sex Characteristics/

5. sex based.ab,kf,ti.

6. sex distribution.ab,kf,ti.

7. sex factors.ab,kf,ti.

8. sexual dimorphism.ab,kf,ti.

9. female$1.ab,kf,ti.

10. male$1.ab,kf,ti.

11. girl$1.ab,kf,ti.

12. boy$1.ab,kf,ti.

13. (men or man).ab,kf,ti.

14. wom#n.ab,kf,ti.

15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. subarachnoid hemorrhage/

17. subarachnoid hemorrhage.ab,kf,ti.

18. Aneurysmal Sub-arachnoid h?emorrhage.ab,kf,ti.

19. aSAH.ab,kf,ti.

20. ruptured brain aneurysm$1.ab,kf,ti.

21. ruptured cerebral aneurysm$1.ab,kf,ti.

22. ruptured intracranial aneurysm$1.ab,kf,ti.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. risk factors/

25. risk factor$1.ab,kf,ti.

26. smoking/

27. smoking.ab,kf,ti.

28. tobacco use*.ab,kf,ti.

29. hypertension/

30. hypertension.ab,kf,ti.

31. blood pressure/

32. blood pressure.ab,kf,ti.

33. drinking behavior/

34. drinking behavio?r.ab,kf,ti.

35. Alcohol drinking.ab,kf,ti.

36. estrogen/

37. estrogen.ab,kf,ti.

38. oestrogen.ab,kf,ti.

39. cocaine/

40. Cocaine.ab,kf,ti.

41. hypercholesterolemia/

42. Hypercholesterolemia.ab,kf,ti.

43. diabetes mellitus/

44. Diabetes Mellitus.ab,kf,ti.

45. familial stroke.ab,kf,ti.

46. (family history adj5 stroke).ab,kf,ti.

47. hormone replacement therapy/

48. hormone replacement therapy.ab,kf,ti.

49. menarche/

50. menarche.ab,kf,ti.

51. menopause/

52. menopause.ab,kf,ti.

53. premenopause/

54. premenopause.ab,kf,ti.

55. postmenopause/

56. postmenopause.ab,kf,ti.

57. body mass index/

58. body mass index.ab,kf,ti.

59. Ovariectomy/

60. Ovariectomy.ab,kf,ti.

61. oophorectomy.ab,kf,ti.

62. hysterectomy/

63. Hysterectomy.ab,kf,ti.

64. androgen deprivation therapy.ab,kf,ti.

65. breast feeding/

66. breast feeding.ab,kf,ti.

67. erectile dysfunction/

68. Erectile dysfunction.ab,kf,ti.

69. orchiectomy/

70. orchiectomy.ab,kf,ti.

71. Gonadotrophin releasing hormone agonist.ab,kf,ti.

72. androgen antagonist.ab,kf,ti.

73. androgen antagonist/

74. anti androgen.ab,kf,ti.

75. testosterone/

76. testosterone.ab,kf,ti.

77. sex hormone-binding globulin/

78. sex hormone-binding globulin.ab,kf,ti.

79. polycystic kidney disease/

80. autosomal dominant polycystic kidney disease.ab,kf,ti.

81. Marfan syndrome/

82. Marfan syndrome.ab,kf,ti.

83. nicotine/

84. nicotine.ab,kf,ti.

85. caffeine/

86. caffeine.ab,kf,ti.

87. cardiovascular disease/

88. cardiovascular disease.ab,kf,ti.

89. ethnic groups/

90. ethnic groups.ab,kf,ti.

91. ethnicity.ab,kf,ti.

92. social class/

93. social class.ab,kf,ti.

94. socioeconomic status.ab,kf,ti.

95. Exercise/

96. exercise.ab,kf,ti.

97. physical activity.ab,kf,ti.

98. sexual behavior/

99. sexual behavio?r.ab,kf,ti.

100. sexual activity.ab,kf,ti.

101. (location adj4 cerebral aneurysm).ab,kf,ti.

102. (location adj4 brain aneurysm).ab,kf,ti.

103. (location adj4 intracranial aneurysm).ab,kf,ti.

104. (shape adj4 brain aneurysm).ab,kf,ti.

105. (shape adj4 cerebral aneurysm).ab,kf,ti.

106. (shape adj4 intracranial aneurysm).ab,kf,ti.

107. (size adj4 brain aneurysm).ab,kf,ti.

108. (size adj4 cerebral aneurysm).ab,kf,ti.

109. (size adj4 intracranial aneurysm).ab,kf,ti.

110. parity/

111. parity.ab,kf,ti.

112. gravidity/

113. gravidity.ab,kf,ti.

114. pregnancy/

115. pregnancy.ab,kf,ti.

116. Age Factors/

117. age.ab,kf,ti.

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Chapter 4: Sex Differences in Aneurysmal Subarachnoid Haemorrhage (aSAH): Aneurysm characteristics, Neurological complications, and Outcome

4.1 Preface

This thesis chapter is published as a paper in *Acta Neurochirurgica* (see Appendix D)

Authors note – at the time of analysis and preparation of this manuscript, data on survival out to 12 months was not available for this cohort. The data on survival to 12 months are presented in the following chapter. There are some differences between this chapter and the published version of this manuscript due to integrating supplements to assist with readability of the thesis.

4.2 Abstract

Background: Women are over-represented in aSAH cohorts but whether their outcomes differ to men remains unclear. We examined if sex differences in neurological complications and aneurysm characteristics contributed to aSAH outcomes.

Methods: In a retrospective cohort (2010-2016) of all aSAH cases across two hospital networks in Australia, information on severity, aneurysm characteristics and neurological complications (rebleed before/after treatment, post-operative stroke <48 hours, neurological infections, hydrocephalus, seizures, delayed cerebral ischaemia [DCI], cerebral infarction) were extracted. We estimated sex differences in (1) complications and aneurysm characteristics using chi square/t tests and (2) outcome at discharge (home, rehabilitation or death) using multinomial regression with and without matching on pre-stroke confounders.

Results: Among 577 cases (69% women, 84% treated) aneurysm size was greater in men than women and DCI more common in women than men. In unadjusted log multinomial regression, women had marginally greater discharge to rehabilitation (RRR 1.15 95% CI 0.90-1.48) and similar likelihood of in-hospital death (RRR 1.02 95% CI 0.76-1.36) versus discharge home. Pre-stroke confounders (age, hypertension, smoking status) explained greater risk of death in women (rehabilitation RR 1.13 95% CI 0.87-1.48); death (RRR 0.75 95% CI 0.51-1.10). Neurological complications (DCI and hydrocephalus) were covariates explaining some of the greater risk for poor outcomes in women (rehabilitation RRR 0.87 95% CI 0.69-1.11; death RRR 0.80 95% CI 0.52-1.23). Results were consistent in propensity score matched models.

Conclusion: The marginally poorer outcome in women at discharge was partially attributable to pre-stroke confounders and complications. Improvements in the managing complications could improve outcomes.

4.3   Introduction

In contrast to other stroke types, women have a greater incidence of aneurysmal subarachnoid haemorrhage (aSAH) than men.[43, 171] In some studies female sex has been shown to be an independent determinant of poor outcome following aSAH, with greater 30-day case-fatality [66] and poorer up to 2-year outcome[89, 194-196] than men. Others have reported that sex is not a prognostic factor for outcome following aSAH.[52, 64, 69, 85] Few studies have been specifically designed to examine sex differences in outcome after aSAH. In our previous research including mostly ischaemic strokes, we determined that characteristics before stroke such as age and co-morbidities but also more modifiable factors such as stroke severity and aspects of clinical management were contributing to poorer outcomes for women compared to men.[126, 197] There has been limited research exploring patient-level factors that may explain sex differences in outcome after aSAH. Such findings are potentially important clinically because they may lead to sex-specific interventions to improve management and outcome.

Aneurysm characteristics and neurological complications predict outcome after aSAH. [52, 85, 89] There is also some evidence that these vary by sex, suggesting that these could mediate any sex differences in outcome after aSAH. Delayed Cerebral Ischaemia (DCI) occurs in nearly 30% of patients [198] and is the most important cause of mortality and morbidity for aSAH. While some authors have reported that the incidence of DCI was greater in women than men, [199, 200] authors of a systematic review concluded that there was limited evidence of a sex difference but that only one out of four studies was of high quality.[201] Among other neurological complications, hydrocephalus has been reported to be more frequent in women than men [109], rebleeding more common in men than women,[202] while no detectable sex difference has been reported for seizures. [203] Aneurysm characteristics including location (e.g. posterior circulation) [52] and larger size [52, 85, 196] are associated with poor outcome. Some researchers have reported sex differences in site and location of ruptured aneurysm.[50, 52, 69] Most of these studies were not designed to examine sex differences in complications, had small sample sizes and few used standardised assessment of complications. No studies though have explored how differences in aneurysm characteristics between men and women may influence outcome.

We therefore aimed to examine sex differences in (1) neurological complications, (2) aneurysm characteristics, (3) discharge outcomes including the role of complications and aneurysm characteristics in any differences observed. We hypothesised that compared to men, women

would more often have unfavorable aneurysm characteristics and complications that would result in worse outcomes after aSAH.

4.4 Methods

This was a retrospective cohort study of all patients with aSAH across two tertiary referral hospital networks (Tasmania, population ~500,000 and South East Victoria, population ~1.2 million) in Australia from 1st January 2010 to 31st December 2016. Both hospitals are comprehensive cerebrovascular centres, receiving patients who experience aSAH from a network of urban, regional and rural hospitals. This study was approved by the Human Research Ethics Committee in Victoria (RES-18-0000-036A) and Tasmania (H0014563). Potential cases were identified using multiple overlapping sources including admission, discharge and ward lists for emergency, neurosurgical and radiology departments across the tertiary centres and referring hospitals. A combination of International Classification of Diseases 10 codes (160.0-160.9, 167.1 and 169.0), as either a primary or secondary diagnosis, and keyword searches were used to ascertain potential cases. A standardised extraction form using data from radiology, pathology and surgical reports, as well as the medical record were used to confirm first ever aSAH. Potential cases were coded by one researcher in each site, and a neurosurgeon and/or an interventional neuroradiologist confirmed the diagnoses and resolved any discrepancies. Following detailed review of medical records patients with unruptured aneurysms were excluded, and only those with confirmed SAH included in the final sample.

The presence of subarachnoid haemorrhage was confirmed on either non-contrast CT-Brain or xanthochromia on lumbar puncture. CT-angiography, digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) were then used to find a cause, including an aneurysm, and characterise it. We excluded cases with previous history of aSAH and other causes of subarachnoid haemorrhage including arteriovenous malformations (AVMs), trauma, amyloid angiopathy and non-aneurysmal SAH. The latter were only excluded where, despite multiple series of imaging tests, a cerebral aneurysm could not be demonstrated. After verifying the aneurysmal cause of SAH, information was extracted from the medical record and captured in REDCap. [204]

4.4.1 Covariates

4.4.1.1 Aneurysm characteristics

We extracted information for the side of aneurysm, anterior or posterior part of the circulation, site on Circle of Willis and maximal size in millimetres. The information was collected from neuroradiological reports from neuroimaging (e.g. CT scans and DSAs). The location of the aneurysm was categorised into five groups, including posterior communicating artery, internal carotid artery (anterior choroidal and internal carotid excluding posterior communicating), anterior cerebral artery (A1 pre-communicating part of anterior cerebral artery which originates from the terminal bifurcation of the internal carotid artery, extending almost 14 mm in length, terminating at the anterior communicating artery and pericallosal), middle cerebral artery (M1 which is the horizontal segment of middle cerebral artery, at bifurcation and, distal middle cerebral artery) and Posterior circulation (posterior cerebral branches, basilar, vertebral, superior cerebellar, anterior inferior cerebellar, posterior inferior cerebellar, vertebrobasilar junction). We categorized aneurysm size into four groups based on previous literature: $\leqslant$ 6.9mm, 7-9.9mm, 10-19.9mm and $\geqslant$20mm [205]. In a small number of patients, the size of aneurysm could not be determined due to absence of information in the respective records, and so these were categorised as missing.

4.4.1.2 Complications

Neurological complications were abstracted based on the National Institute of Neurological Disorders and Stroke definitions (NINDS).[108] These included post-operative stroke within 48 hours, post-treatment neurological infections, rebleed, hydrocephalus (defined by the presence of an intervention), seizures, DCI (based on clinical criteria) and cerebral infarction (based on radiological evidence). Treatments for complications were also extracted. These included ventriculostomy/external ventricular drains (EVD) or shunt placement for pre- and post-operative hydrocephalus, and endovascular balloon angioplasty or intra-arterial vasodilators for DCI.

4.4.2 Outcome

Outcome was categorized according to the discharge destination after acute admission which included discharge to home, discharge to rehabilitation or in-hospital death.

4.4.3 Patient characteristics

Patient characteristics, pre-stroke clinical and behavioural factors' details were extracted from medical records including age, smoking status (current smoker, ex-smoker and non-smoker), history of high blood pressure (antihypertensive medications on admission and/or recorded history), World Federation of Neurological Surgeons severity grading (WFNS from neurosurgical or neuroradiological records) and Modified Fisher scores (higher score depicted worse prognosis from neurosurgical or neuroradiological records), medications (antihypertensive agents and nimodipine), type of treatment for aneurysm (coiling or clipping) and hospital network.

4.4.4 Statistical analysis

We examined sex differences in the aneurysm characteristics and neurological complications using Pearson's chi square for categorical variables and t-test for continuous variables.

We used log multinomial regression to estimate the relative risk ratio (RRR ±95% confidence interval [CI]) of discharge to rehabilitation or death in-hospital compared to discharged home for women compared to men. We built two multivariable models: the first to estimate the effect of sex on outcome independent of 'pre-stroke confounding factors' such as demographic and clinical factors (Model 1), and the second to include 'covariates' which include aneurysm characteristics and complications to examine their additional effect (Model 2). We identified potential pre-stroke confounding factors to include in our models that were known to be associated with poor outcome from existing literature as well as analyses of study factors (e.g. demographics, pre-stroke health or clinical factors). We examined variables for confounder adjusted model if they were different by sex in our study. We used purposeful model building to create a model adjusted for pre-stroke confounders selecting to include a variable in the model when (1) the covariate was associated with sex (p-value≤0.25), (2) the covariate was associated with the outcome (p-value≤0.25), and (3) the covariate that changed the effect of sex on the outcome by ≥10%. [197, 206] As our objective was to examine whether aneurysm characteristics or complications contributed to sex differences in discharge destination, we entered aneurysm characteristics and complications that were different by sex as covariates into the confounder adjusted model. Changes in the magnitude of effect for sex on the outcome when adjusted for aneurysm characteristics or complications would suggest these factors

contribute to sex differences in outcome. We explored interactions between sex and covariates using product terms in the final multivariable models.

We performed sensitivity analyses using propensity score matching as an alternative to the classical confounder adjusted models. We created propensity scores to match men and women based on pre-stroke confounders different by sex, and then applied weights based on the propensity score to the multinomial logistic regression. Aneurysm characteristics and complications that differed by sex were entered into the weighted model as covariates. Analysis was performed in statistical software Stata15 (StataCorp LLC, Texas, USA) and a two-sided p-value<0.05 was considered statistically significant.

4.5 Results

There were 577 confirmed cases of aSAH. Women were overrepresented more than men(69% of cases; **Table 4-1**). Data were generally complete with <1% missing details of discharge destination and <10% missing details of aneurysm characteristics or complications.

4.5.1 Aneurysm characteristics

In both sexes, aneurysms were more common in the anterior than posterior circulation (**Table 4-2** and **Figure 4-1**). There were more midline aneurysms in men (42%) than women (31%) and more left-sided aneurysms in women (24%) than men (32%). There were sex differences in the anatomical location of aneurysm (p=0.001). Anterior cerebral artery location (42%) was the most common site in men followed by middle cerebral artery (20%) and posterior circulation (20%). In women, anterior cerebral artery (33%), posterior communicating artery (20%) and posterior circulation (20%) were the most common positions for the rupture of the aneurysm. The mean size of aneurysm was smaller in women than men (p=0.02). More men (26%) than women (16%, p=0.03) had an aneurysm size >10mm.

4.5.2 Aneurysmal repair

Aneurysm was repaired by either clipping or coiling or both. There was no sex difference in the type of intervention (**Table 4-1**).

4.5.3 Complications

Neurological complications were common, with 61% of men and 69% of women having at least one complication (**Table 4-3**). We were unable to detect a difference between men and women in post-operative stroke within 48 hours, early rebleeding and after intervention, seizure,

meningitis, cerebral infarction and ventriculitis. Hydrocephalus (Men 46%, Women 54%, p=0.06) and DCI were less common in men compared to women (Men 25%, Women 35%, p=0.003).

4.5.4   Treatment for DCI

In total 130 (33%) women and 42 (23%) men experienced DCI. Among those with DCI, women (55%) more often received treatment than men (40%; p=0.08, **Table 4-3**). A total of 71 (55%) women and 17 (40%) men with confirmed DCI and/or cerebral infarction received some type of endovascular management. Among these, more women (93%) received intra-arterial vasodilators (nicardipine, papaverine and nimodipine) than men (65%). Mechanical treatment of endovascular angioplasty was more common in men (35%) than women (7%, p=0.001).

4.5.5   Treatment for hydrocephalus

Ventriculostomy was performed in 46% men and 54% women (p=0.06), while shunt placement was conducted in 7% of men and 12% of women (p=0.22; **Table 4-3**).

Table 4-1 Characteristics of cohort

Variable	Men[§] N=179		Women[§] N=398		P-value
	N	(%)	N	(%)	
No of patients (%)	179	(31)	398	(69)	
Mean age (SD)	54.44 (14.94)		57.78 (15.34)		0.01*
Age category					0.18
≤55 years	94	(53)	185	(46)	
>55years	85	(47)	213	(54)	
Smoking					0.10
Current smoker	92	(51)	171	(43)	
Ex-smoker	25	(14)	36	(9)	
Non-smoker	32	(18)	90	(23)	
Missing	30	(17)	101	(25)	
Hypertension					0.006**
Yes	61	(34)	187	(47)	
No	110	(61)	200	(50)	
Missing	8	(4)	11	(3)	
Charlson comorbidity index					0.23
0 or 1	157	(88)	334	(84)	
≥ 2	22	(12)	64	(16)	
States					0.48
Victoria	106	(59)	248	(62)	
Tasmania	73	(41)	150	(38)	
WFNS					0.37
I	88	(49)	166	(42)	
II	28	(16)	72	(18)	
III	6	(3)	20	(5)	
IV	12	(7)	39	(10)	
V	43	(24)	91	(23)	
Missing	2	(1)	10	(3)	
Modified Fisher grade					0.76
0	2	(1)	7	(2)	
1	17	(10)	32	(8)	
2	8	(4)	9	(3)	
3	36	(20)	74	(19)	
4	100	(56)	219	(58)	
Missing	16	(9)	61	(11)	
Type of intervention					0.65
Clipping	57	(39)	126	(37)	
Coiling	88	(60)	208	(61)	
Both coiling and clipping	2	(1)	2	(1)	
Not treated	32	(17)	59	(14)	
Missing	0	(0)	3	(0.75)	
Discharge Destination					0.36
Home	73	(41)	138	(35)	

Rehabilitation	58	(32)	148	(37)
Death	48	(27)	108	(27)
Unknown	0	(0)	4	(1)

§Number and (%), unless otherwise indicated
WFNS: World Federation of Neurological Surgeons grading

Table 4-2 Sex Differences in Aneurysm-Specific Findings

Aneurysm specific findings	Men[§] N=179		Women[§] N=398		P-value
	N	%	N	%	
Aneurysm identified	172	(94)	376	(94)	
Posterior or Anterior					0.27
Posterior	38	(21)	64	(16)	
Anterior	134	(75)	313	(79)	
Unknown	7	(4)	21	(5)	
Side of Aneurysm					0.03*
Right	54	(30)	123	(31)	
Left	43	(24)	129	(32)	
Midline	75	(42)	124	(31)	
Unknown	7	(4)	22	(6)	
Location of aneurysm[¶]					0.001*
Pcomm	13	(7)	81	(20)	
Internal Carotid	12	(6)	37	(9)	
ACho	2	(1)	7	(2)	
ICA	10	(5)	30	(7)	
Anterior Cerebral	74	(42)	129	(33)	
ACA-A1	5	(3)	20	(5)	
ACA-Acomm	64	(36)	94	(24)	
ACA-pericallosal	5	(3)	15	(4)	
Middle Cerebral	36	(20)	65	(16)	
MCA -M1	17	(9)	25	(6)	
MCA-at bifurcation	18	(10)	35	(9)	
MCA-distal MCA	1	(0.5)	5	(1)	
Posterior Circulation	37	(20)	66	(20)	
PCA-distal	2	(1)	0	(0)	
P2	2	(1)	0	(0)	
P1	0	(0)	1	(0.5)	
Basilar bifurcation	13	(7)	26	(6)	
SCA	3	(2)	2	(0.5)	
Basilar trunk	5	(3)	9	(2)	
AICA	0	(0)	1	(0.25)	
V-B junction	1	(0.5)	1	(0.25)	
Vertebral	3	(2)	10	(2)	
PICA	8	(4)	16	(4)	
Other	0	(0)	0	(0)	
Choroidal	0	(0)	0	(0)	
Unknown	7	(4)	19	(5)	
Size of aneurysm (mean ± SD) (Mean ±SD) mm	7.89(±4.65)		6.93(±4.14)		0.02*
Missing	11	(6)	30	(7)	
Categories of size (mm)					0.03*
≤6.9	83	(46)	214	(54)	
7-9.9	37	(21)	88	(22)	

10-19.9	42	(23)	61	(15)
≥20	6	(3)	5	(1)

§Number and (%), unless otherwise indicated

¶Aneurysm location collapsed to five categories as mentioned in the text

Abbreviations: Posterior communicating, Pcomm; Anterior choroidal, ACho; Internal carotid artery, ICA; Anterior cerebral artery, ACA; Anterior communicating artery, Acomm; Pre-communicating part of ACA, A1; Middle cerebral artery, MCA; Sphenoidal segment of MCA, M1; Posterior cerebral artery, PCA; Pre-communicating part of PCA, P1; Post-communicating part of PCA, P2; Superior cerebellar artery, SCA; Anterior inferior cerebellar artery, AICA; Vertebrobasilar junction, V-B junction; Posterior inferior cerebellar artery, PICA

Table 4-3 Complications following aSAH

Complications	Men[§] N=179		Women[§] N=398		P-value
	N	%	N	%	
Any neurological complication					0.05*
Yes	110	(61)	275	(69)	
No	69	(39)	119	(30)	
Missing	0	(0)	4	(1)	
Post-op stroke within 48 hours					0.59
Yes	34	(19)	66	(17)	
No	144	(80)	322	(81)	
Unknown	1	(1)	10	(3)	
Early or before treatment rebleed					0.94
Yes	14	(8)	30	(8)	
No rebleed	165	(92)	362	(91)	
Unknown	0	(0)	6	(1)	
Rebleed after treatment					0.42
Yes, confirmed/suspected	3	(2)	9	(3)	
No rebleed	175	(97)	381	(95)	
Unknown	1	(1)	8	(2)	
Hydrocephalus					0.06
Yes	83	(46)	215	(54)	
No	95	(53)	176	(44)	
Unknown	1	(1)	7	(2)	
DCI (clinical deterioration)					0.003**
Yes	34	(19)	122	(31)	
No	135	(75)	253	(64)	
Unknown	10	(6)	23	(5)	
Cerebral Infarction					0.51
Yes	35	(20)	85	(21)	
No	137	(76)	287	(72)	
Unknown or missing	7	(4)	26	(6)	
Neurological Infection					0.24
Meningitis/Ventriculitis	14	(8)	43	(11)	
Non-neurological infections or no infection	164	(92)	346	(87)	
Unknown	1	(1)	9	(2)	
Seizure					0.37
Yes	12	(7)	28	(7)	
No	165	(92)	358	(90)	
Unknown	2	(1)	12	(3)	
Management of complications					
Endovascular therapy for DCI/ cerebral infarction[†]					0.08
No	24	(57)	54	(41)	
Yes	17	(40)	71	(55)	
Missing	1	(2)	5	(4)	

Complications	Men[§] N=179		Women[§] N=398		P-value
	N	**%**	**N**	**%**	
Type of endovascular intervention for DCI/Cerebral infarction					0.001 **
Balloon angioplasty	6	(35)	5	(7)	
Intraarterial Vasodilator	11	(65)	66	(93)	
Ventriculostomy					0.06
Yes	82	(46)	213	(54)	
No	97	(54)	179	(45)	
Missing	0	(0)	6	(1)	
Shunt placement					0.22
Yes	13	(7)	46	(12)	
No	163	(91)	342	(86)	
Missing	3	(2)	10	(2)	

[§]Number and (%), unless otherwise indicated

[†]n=42 men and n=130 women had DCI and/or cerebral infarction

[††]Denominator is n=17 men and n=71 women with endovascular intervention for DCI/cerebral infarction

Figure 4-1 Distribution of Aneurysm site in men and women

Posterior communicating, Pcomm
Internal carotid artery, ICA
Anterior cerebral artery, ACA
Middle cerebral artery, MCA
Posterior circulation aneurysms, Posterior

4.5.6   Sex differences in poor outcome

Regarding sex differences in outcome, more men (40.7%) went home compared to women (34.6%) while more women were discharged to rehabilitation (men 32.4% vs women 37.1%) or died in-hospital (men 26.8% vs women 27.1%).

In univariable analysis including all people with aSAH, women compared to men had a marginally greater risk of being discharged to rehabilitation (RRR 1.15 95% CI 0.90-1.48) and similar likelihood of in-hospital death (RRR 1.02 95% CI 0.76-1.36) versus being discharged to home (**Table 4-4**). Potential pre-stroke confounding factors and covariates of aneurysm characteristics and neurological complications that were different between the sexes were analysed for association with the outcome. Age, DCI and hydrocephalus were associated with discharge to rehabilitation and in hospital death while hypertension history and size of the aneurysm were associated with in-hospital death only. We identified age, hypertension history and smoking status were different between men and women whereas severity scores, comorbidities and treatment modalities were similar between the sexes. In model 1, adjusted for pre-stroke confounding factors (**Table 4-4**), women compared to men had a marginally greater risk of being discharged to rehabilitation (1.13 95% CI 0.87-1.48, p=0.34) and lesser risk of in-hospital death (0.75 95% CI 0.51-1.10, p=0.14). In model 2 (**Table 4-4**), adjusted for covariates (DCI and hydrocephalus), women had a somewhat lesser risk of being discharged to rehabilitation (0.87 95% CI 0.69-1.11, p=0.28) and death (0.80 95% CI 0.52-1.23, p=0.32) where age, hypertension history, presence of DCI and hydrocephalus were independently associated with death and discharge to rehabilitation. There were no interactions between sex and the other variables included in the final model.

 In the sensitivity analyses on the matched analysis of men and women (**Table 4-5**), the relative risk ratio for discharge to rehabilitation was 1.19 (95% CI 0.75-1.89, p=0.44) and for in-hospital death was 0.84 (95% CI 0.48-1.48, p=0.56). In covariate adjusted analysis, the risk of discharge to rehabilitation was 0.84 (95% CI 0.50-1.39, P=0.50) and the risk of death was 0.73 (95% CI 0.40-1.33, p=0.31). There were slight differences in the risk, but the confidence intervals were wide. The estimates were nearly consistent with log multinomial regression.

Regarding missing data, an analysis of the characteristics associated with missing data showed that only the proportion dying during hospitalisation differed between those with and without data on complications or details of the aneurysm (**Table 4-6**, **Table 4-7** and **Table 4-8**).

Table 4-4 Relative Risk ratio for discharge home or rehabilitation versus death in women compared to men in log-multinomial regression analysis

Variables	All patients N=577					
	Rehabilitation			Death		
	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)
Female sex	1.15 (0.90-1.48)	1.13 (0.87-1.48)	0.87 (0.69-1.11)	1.02 (0.76-1.36)	0.75 (0.51-1.10)	0.80 (0.52-1.23)
Aneurysm characteristics						
Site						
Anterior Cerebral	Ref			Ref		
Internal Carotid	0.98 (0.65-1.48)			1.40 (0.85-2.30)		
Posterior Communicating	0.83 (0.58-1.18)			1.12 (0.72-1.74)		
Middle Cerebral	0.99 (0.72-1.34)			1.36 (0.91-2.03)		
Posterior Circulation	1.12 (0.83-1.50)			1.36 (0.91-2.03)		
Size of aneurysm (mm)	0.99 (0.96-1.01)			**1.04 (1.02-1.05)**		
Neurological Complications						
Hydrocephalus	**2.50 (1.91-3.27)**		**1.68 (1.27-2.23)**	**1.71 (1.27-2.29)**		**1.97 (1.27-3.05)**
DCI (Clinical deterioration)	**2.72 (2.20-3.36)**		**2.80 (2.02-3.90)**	**0.63 (0.42-0.91)**		0.95 (0.53-1.69)
Confounding factors						
Age	**1.00 (0.99-1.02)**	**1.01 (0.99-1.02)**	**1.01 (1.00-1.02)**	**1.01 (1.01-1.02)**	**1.02 (1.01-1.04)**	**1.04 (1.02-1.06)**
Smoking						
Non-smoker	Ref					
Current	0.97	1.06	0.87	0.89	1.16	1.51

Variables	All patients N=577					
	Rehabilitation			Death		
	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)
Smoker	(0.73-1.26)	(0.79-1.42)	(0.70-1.09)	(0.57-1.37)	(0.74-1.81)	(0.90-2.55)
Ex-smoker	1.09	1.19	1.05	0.87	0.93	0.79
	(0.76-1.58)	(0.81-1.73)	(0.73-1.51)	(0.46-1.65)	(0.49-1.77)	(0.41-1.51)
Hypertension						
No	Ref			Ref		
Yes	1.15	0.99	**1.33**	**1.81**	**1.61**	**1.85**
	(0.89-1.38)	(0.78-1.27)	**(1.05-1.70)**	**(1.35-2.41)**	**(1.12-2.33)**	**(1.17-2.91)**

Model 1 (adjusted for pre-stroke confounding factors)

Model 2 (adjusted for pre-stroke confounding factors and covariates)

*Adjusted for hospital network

Confounders included age, hypertension history and smoking status and covariates included DCI and hydrocephalus

Table 4-5 Relative risk ratio for discharge home or rehabilitation versus death in women compared to men in multinomial logistic regression analysis

Variables	All patients N=577			
	Rehabilitation		Death	
	RRR (95% CI) *	RRR (95% CI) **	RRR (95% CI) *	RRR (95% CI) **
Female sex	1.19 (0.75-1.89)	0.84 (0.50-1.39)	0.84 (0.48-1.48)	0.73 (0.40-1.33)
Hydrocephalus		**4.14 (2.47-6.94)**		**3.16 (1.75-5.69)**
DCI (Clinical deterioration)		**6.00 (3.13-11.49)**		1.94 (0.92-4.08)

*Matched on pre-stroke confounders different by sex
 **Adjusted for covariates and hospital network
Confounders included age, hypertension history and smoking status and covariates included DCI and hydrocephalus

Table 4-6 Comparison of characteristics for people with complete and missing data on complications

Variable		No missing data on complications§ (N=526)		Any missing data on complications§ (N=51)		P-value
		N	(%)	N	(%)	
Age	<=55	252	(48)	27	(53)	0.49
	>55	274	(52)	24	(47)	
Sex	Men	165	(31)	14	(27)	0.56
	Women	361	(69)	37	(73)	
Hypertension history	Yes	228	(43)	20	(39)	0.68
	No	282	(54)	28	(54)	
	Missing	16	(3)	3	(5)	
Smoking	Current	243	46	20	39	0.25
	Ex	58	11	3	6	
	Non	108	20	14	27	
	Missing	117	22	14	27	
WFNS	I	233	(44)	21	(41)	0.50
	II	96	(18)	4	(8)	
	III	24	(4)	2	(4)	
	IV	47	(9)	4	(9)	
	V	120	(23)	14	(27)	
	Missing	6	(1)	6	(12)	
Fisher scale	0	8	(1)	0	(16)	
	1	42	(7)	8	(0)	0.10
	2	18	(3)	0	(0)	

Variable		No missing data on complications[§] (N=526)		Any missing data on complications[§] (N=51)		P-value
		N	(%)	N	(%)	
	3	104	(19)	6	(12)	
	4	306	(58)	26	(51)	
	Missing	48	(10)	11	(21)	0.06
Clipping	Yes	177	(67)	10	(19)	
	No	349	(33)	39	(76)	
	Missing	0	(0)	2	(4)	
Coiling	Yes	276	(48)	24	(47)	0.74
	No	250	(52)	24	(47)	
	Missing	0	(0)	3	(5)	
Posterior /Anterior	Posterior	90	(18)	12	(23)	0.40
	Anterior	414	(77)	33	(65)	
	Missing	22	(5)	6	(12)	
Side	Midline	184	(35)	15	(29)	0.1
	Right	160	(30)	17	(33)	
	Left	159	(30)	13	(25)	
	Missing	23	(4)	6	(12)	
Site aneurysm	ACA	187	(35)	16	(31)	0.09
	ICA	46	(9)	3	(6)	
	Pcomm	86	(16)	8	(6)	
	MCA	97	(18)	4	(8)	
	Posterior	89	(17)	15	(30)	
	Missing	21	(4)	5	(10)	

Variable		No missing data on complications[§] (N=526)		Any missing data on complications[§] (N=51)		P-value
		N	(%)	N	(%)	
Size	Mean (SD)	7.30 (4.37)		6.39 (3.68)		0.19
	Measured	495	(94)	41	(80)	
	Missing	31	(6)	10	(20)	
Discharge destination	Home	197	(37)	14	(27)	<0.001***
	Rehab	176	(34)	7	(14)	
	Another hospital	14	(2)	9	(17)	
	Died	139	(26)	17	(33)	
	Missing	0	(0)	4	(8)	
Ambulance transfer[¶]	Yes	419	(79)	35	(68)	0.74
	No	95	(18)	9	(17)	
	Missing	12	(3)	7	(13)	
Inter-hospital transfer	Admitted to same hospital	280	(53)	21	(41)	0.003**
	Transferred to another hospital	243	(46)	28	(55)	
	Died/Sent home	3	(0.5)	1	(2)	
	Missing	0	(0)	1	(2)	

[§]Number and (%), unless otherwise indicated;[¶]Ambulance transfer refers to initial arrival by ambulance; WFNS: World Federation of Neurological Surgeons
ACA: Anterior cerebral artery, ICA: Internal carotid artery, Pcomm: Posterior communicating, MCA: Middle cerebral artery, Posterior: Posterior circulation

Table 4-7 Comparison of characteristics for people with complete and missing data on aneurysm specific findings

Variable		No missing data on aneurysm characteristics§ (N=524)		Any missing data on aneurysm characteristics§ (N=53)		P-value
		N	(%)	N	(%)	
Age	<=55	250	(49)	29	(54)	0.33
	>55	274	(51)	24	(45)	
Sex	Men	165	(32)	14	(26)	0.44
	Women	359	(68)	39	(73)	
Hypertension history	Yes	225	(43)	23	(43)	0.92
	No	282	(54)	28	(53)	
	Missing	17	(3)	2	(4)	
Smoking	Current	244	(46)	19	(36)	0.59
	Ex	58	(11)	3	(6)	
	Non	111	(21)	11	(21)	
	Missing	111	(21)	20	(37)	
WFNS	I	237	(45)	17	(32)	0.36
	II	93	(18)	7	(13)	
	III	25	(4)	1	(2)	
	IV	46	(8)	5	(9)	
	V	118	(22)	16	(30)	
	Missing	5	(1)	7	(13)	
Fisher scale	0	6	(1)	2	(4)	0.12
	1	47	(8)	3	(6)	
	2	18	(3)	0		

Variable		No missing data on aneurysm characteristics[§] (N=524)		Any missing data on aneurysm characteristics[§] (N=53)		P-value
		N	(%)	N	(%)	
	3	105	(20)	5	(9)	
	4	301	(57)	31	(58)	
	Missing	47	(9)	12	(22)	
Clipping	Yes	170	(33)	17	(32)	0.89
	No	354	(67)	34	(64)	
	Missing	0	(0)	2	(3)	
Coiling	Yes	285	(54)	15	(28)	0.001**
	No	238	(45)	36	(67)	
	Missing	1	(0.19)	2	(3)	
Post-op stroke within 48 hrs	Yes	95	(18)	6	(11)	0.34
	No	424	(81)	41	(77)	
	Missing	5	(1)	6	(11)	
Early or before treatment rebleed	Yes	40	(7)	4	(7)	0.82
	No	484	(91)	43	(81)	
	Missing	5	(1)	6	(11)	
Rebleed after treatment	Yes	12	(2)	2	(3)	0.40
	No	509	(97)	45	(85)	
	Missing	3	(1)	6	(11)	
Neurological Infection	Yes	55	(10)	2	(3)	0.16
	No	465	(88)	45	(84)	
	Missing	4	(2)	6	(11)	

Variable		No missing data on aneurysm characteristics[§] (N=524)		Any missing data on aneurysm characteristics[§] (N=53)		P-value
		N	(%)	N	(%)	
Seizure	Yes	40	(7)	1	(2)	0.16
	No	477	(91)	45	(85)	
	Missing	7	(1)	7	(13)	
DCI (Clinical deterioration)	Yes	149	(28)	7	(13)	0.05
	No	351	(67)	37	(69)	
	Missing	24	(5)	9	(16)	
Cerebral Infarction	Yes	116	(22)	4	(7)	0.03*
	No	384	(73)	40	(75)	
	Missing	24	(4)	9	(16)	
Hydrocephalus	Yes	278	(53)	20	(38)	0.09
	No	242	(46)	29	(55)	
	Missing	4	(1)	4	(7)	
Discharge destination	Home	210	(37)	1	(7)	0.001**
	Rehab	182	(32)	1	(7)	
	Another hospital	22	(4)	1	(7)	
	Died	145	(26)	11	(78)	
	Missing	4	(1)	0	(0)	
Ambulance transfer[¶]	Yes	414	(79)	40	(75)	0.71
	No	96	(18)	8	(15)	
	Missing	14	(2)	5	(9)	

Variable		No missing data on aneurysm characteristics[§] (N=524)		Any missing data on aneurysm characteristics[§] (N=53)		P-value
		N	(%)	N	(%)	
Inter-hospital transfer	Admitted to same hospital	277	(53)	24	(45)	<0.001***
	Transferred to another hospital	245	(46)	26	(49)	
	Died/Sent home	2	(0.3)	2	(3)	
	Missing	0	(0)	1	(2)	

[§]Number and (%), unless otherwise indicated;[¶]Ambulance transfer refers to initial arrival by ambulance
WFNS: World Federation of Neurological Surgeons

Table 4-8 Comparison of characteristics for people with complete and missing data on discharge destination

Variable		No Missing data on discharge destination§ (N=573)		Any Missing data on discharge destination§ (N=4)		P-value
		N	(%)	N	(%)	
Age	<=55	276	(48)	3	(75)	0.35
	>55	297	(51)	1	(25)	
Sex	Men	179	(31)	0	(0)	0.31
	Women	394	(69)	4	(100)	
Hypertension history	Yes	246	(43)	2	(50)	0.43
	No	309	(54)	1	(25)	
	Missing	18	(3)	1	(25)	
Smoking	Current	261	(45)	2	(50)	0.78
	Ex	61	(11)	0	(0)	
	Non	121	(21)	1	(25)	
	Missing	130	(22)	1	(25)	
WFNS	I	254	(44)	0	(0)	
	II	100	(17)	0	(0)	
	III	26	(4)	0	(0)	-
	IV	51	(8)	0	(0)	
	V	134	(23)	0	(0)	
	Missing	8	(1)	4	(100)	
Fisher scale	0	8	(1)	0	(0)	1.000
	1	50	(9)	0	(0)	
	2	18	(3)	0	(0)	

Variable		No Missing data on discharge destination[§] (N=573)		Any Missing data on discharge destination[§] (N=4)		P-value
		N	(%)	N	(%)	
	3	110	(19)	0	(0)	1.000
	4	331	(57)	1	(25)	
	Missing	56	(9)	3	(75)	
Clipping	Yes	186	(32)	1	(25)	1.000
	No	385	(67)	3	(75)	
	Missing	2	(0.35)	0	(0)	
Coiling	Yes	297	(51)	3	(75)	0.62
	No	273	(47)	1	(25)	
	Missing	3	(0.5)	0	(0)	
Posterior /Anterior	Posterior	102	(17)	0	(0)	1.00
	Anterior	445	(77)	2	(50)	
	Missing	26	(4)	2	(50)	
Side	Midline	198	(34)	1	(25)	0.76
	Right	177	(30)	0	(0)	
	Left	171	(29)	1	(25)	
	Missing	27	(5)	2	(50)	
Site aneurysm	ACA	202	(35)	1	(25)	0.15
	ICA	49	(8)	0	(0)	
	Pcomm	94	(16)	0	(0)	
	MCA	101	(17)	0	(0)	
	Posterior	101	(17)	3	(75)	
	Missing	26	(4)	0	(0)	

Variable		No Missing data on discharge destination[§] (N=573)		Any Missing data on discharge destination[§] (N=4)		P-value
		N	(%)	N	(%)	
Size	Measured	533	(94)	0	(0)	
	Missing	37	(6)	4	(100)	
Ambulance transfer[¶]	Yes	454	(79)	0	(0)	-
	No	104	(18)	0	(0)	
	Missing	15	(2)	4	(100)	
Inter-hospital transfer	Admitted to same hospital	301	(52)	0	(0)	0.20
	Transferred to another hospital	267	(46)	4	(100)	
	Died/Sent home	4	(1)	(0)	(0)	
	Missing	1	(0.17)	(0)	(0)	
Post-op stroke with 48 hrs	Yes	101	(17)	0	(0)	-
	No	465	(81)	0	(0)	
	Missing	7	(1)	4	(100)	
Early or before treatment rebleed	Yes	44	(7)	0	(0)	-
	No	527	(91)	0	(0)	
	Missing	2	(1)	4	(100)	
Rebleed after treatment	Yes	14	(2)	0	(0)	-

Variable		No Missing data on discharge destination[§] (N=573)		Any Missing data on discharge destination[§] (N=4)		P-value
		N	(%)	N	(%)	
	No	554	(96)	0	(0)	
	Missing	5	(1)	4	(100)	
Neurological Infection	Yes	57	(9)	0	(0)	-
	No	510	(89)	0	(0)	
	Missing	6	(1)	4	(100)	
Seizure	Yes	41	(8)	0	(0)	
	No	522	(91)	0	(0)	
	Missing	10	(1)	4	(100)	-
Clinical deterioration	Yes	156	(27)	0	(0)	-
	No	388	(67)	0	(0)	
	Missing	29	(5)	4	(100)	
Cerebral Infarction	Yes	120	(20)	0	(0)	-
	No	424	(74)	0	(0)	
	Missing	29	(5)	4	(100)	
Hydrocephalus	Yes	298	(52)	0	(0)	0.22
	No	269	(46)	2	(50)	
	Missing	6	(1)	2	(50)	

[§]Number and (%), unless otherwise indicated;[¶]Ambulance transfer refers to initial arrival by ambulanceWFNS: World Federation of Neurological Surgeons
ACA: Anterior cerebral artery, ICA: Internal carotid artery, Pcomm: Posterior communicating, MCA: Middle cerebral artery, Posterior: Posterior circulation

4.6   Discussion

This is the largest study examining the role of sex in short term-outcome following aSAH. Women were older, more often had a history of hypertension and more frequently suffered from DCI and hydrocephalus than men. Sex did not predict outcome, however; women had a marginally greater risk of being discharged to rehabilitation and in-hospital death. The risk of death decreased slightly when pre-stroke confounding factors were taken into account. The risk of poor outcomes in women was explained by age, history of hypertension, presence of DCI and hydrocephalus.

Sex did not predict poor outcomes in our study. Among the few prior studies designed to examine the factors associated with the outcome in aSAH, women have generally been found to have a poorer outcome than men, [196, 207] although not consistently. [52, 65, 69] In one comparable study of 120 people (69% women), although 6-month mortality appeared to be greater in women (28%) than men (16%), this was not apparent in multivariable analysis.[65] In other studies, there was no detectable difference between men and women in the risk of worse outcome at 3 months when adjusting for age, neurological condition on admission, site [52, 69] and size of aneurysm, and length of stay.[52] There is an urgent need for research to improve diagnosis, prevention and treatment of complications after aSAH, particularly DCI and management of hydrocephalus, which could lead to improved outcome.

DCI and hydrocephalus were more common in women than in men. Our finding is in agreement with some studies [109, 199, 200] but contrasts with others. [201, 208] The risk of DCI is associated with the size of initial bleed and poor WFNS grades [209] but its pathophysiology remains unexplained. [198] The greater risk of DCI in women could be related to physiological factors including smaller vessels compared to men that result in high sheer wall stress inducing vascular injury and ultimately leading to ischaemia.[199] The explanation for our finding that hydrocephalus was more common in women than men is unclear, but some authors suggest a possible role of estrogen.[210] Complications were very common after aSAH and there are limited clinical guidelines to guide prevention, diagnosis and management.

There were sex differences in the location of ruptured aneurysms. The anterior communicating artery was the most common site in men, while anterior communicating and posterior communicating arteries were the most common locations in women. This is consistent with previous studies that tended to be single-centre or regionally focused.[50, 52, 211] These sex differences in aneurysm site on Circle of Willis may be due to morphological, embryological

and physiological factors. In a study based on sex differences specific to morphology of ruptured aneurysms of anterior communicating artery, the authors noticed that morphological measures of the aneurysm such as aneurysm size, flow angles and vessel angles were greater in men than women. [212] These morphological differences might be the reason for more anterior communicating ruptured aneurysms in men than women. [212] Anatomical variations in the Circle of Willis, which are linked to a higher rate of aneurysm rupture, have been linked to differences in aneurysm distribution in men and women.[213] Type A variation when there is an absence of unilateral A1 segment (pre-communicating part of anterior cerebral artery) was more common in men, while women more often had Type P variations when the fetal type of posterior cerebral artery originates from the internal carotid artery, and thus has been linked to internal carotid artery aneurysm.[214] Considering physiological factors, authors of another study found that vessel diameters were greater in men than in women. There was more sheer wall stress in women [215] mostly at bifurcations, and this could be a potential reason for more aneurysms in women. Although posterior circulation aneurysms and greater aneurysmal size were considered predictors of unfavorable outcomes in previous studies,[85, 216] in our study most aneurysms were located in the anterior circulation. Despite the sex differences in location and size of the ruptured aneurysm, we could not detect any association of these findings with outcome in the covariate adjusted analyses.

Although our study was focused on sex differences in aSAH, the study also provides more general insights into predictors of poor outcome after aSAH from a large, multicentre, contemporary cohort ascertained using sound epidemiological methods. We observed that risk factors like history of hypertension was more common in women and smoking was more frequent in men. A poor risk factor profile leads to early deaths from aSAH.[217] These behavioral factors have been linked to unfavorable outcomes[100, 218] and are also a cause of various neurological complications after aSAH.[51, 218, 219] Older age was also a risk for worse outcomes in our study as supported by others.[85, 86] We reported no significant interaction of sex with age and other covariates in the study for association with the outcome, however, there is a dearth in literature regarding the interaction of sex with other factors while reporting the outcomes after aSAH. In accordance with previous research, patients with DCI [220] and hydrocephalus[221, 222] were more often discharged to rehabilitation, an indicator of greater functional impairment, and had a greater risk of in-hospital death, reinforcing the significance of these complications. Prevention of modifiable risk factors and rapid diagnosis and improvement in the management

of DCI and hydrocephalus is important to prevent death and temporary or permanent disability after aSAH in both sexes, but particularly women given its higher incidence in that group.

There were some limitations of our study. Owing to the low incidence of aSAH, the study was retrospective, which resulted in some missing data for the outcomes of interest ($\leqslant$10%) and risk factors like smoking (25%). As out of hospital deaths were not available for the study, our results are only generalizable to hospitalized patients. The use of discharge outcome is also a limitation of our study, as functional improvement or deterioration from delayed complications may occur following discharge. Examination of other more relevant patient-centred outcomes such as health related quality of life are needed. We also did not have data on severity of angiographic vasospasm which is one of the mechanisms that leads to DCI.[223] Instead, we recorded DCI using the clinical NINDS definition noting that "vasospasm" was often used as an alternate term in medical records. The diagnosis of DCI was confirmed using medical notes, treatment received and confirmation from neurointerventional radiologist. We recorded for hydrocephalus indicated by intervention like ventriculostomy or shunt placement. We further confirmed DCI and hydrocephalus from post-operative notes, imaging and details on treatment related to both complications. Aneurysm characteristics were taken from neuroimaging after rupture, which may result in mis-estimation of aneurysm size, noting that this is a common method used in studies of aSAH.[50, 52]

There were several strengths of the current study. Unlike most previous studies that have been in single centres, we had data from all consecutive cases of radiographically confirmed aSAH across two hospital networks, making our results more generalisable. We had access to clinical and radiological records and only included confirmed cases of aneurysmal rupture. We further included only first ever cases of aSAH, and so our findings were not complicated by ongoing neurological impairments from previous events, different management or outcomes. We used standardised clinical definitions for complications, while aneurysm characteristics were reported by neuroradiologists.

4.6.1 Conclusions

In conclusion, there were more women than men in our cohort of aSAH participants. They were older and more often have a history of hypertension whereas smoking was more common in men. They were found to have a slightly greater likelihood of being discharged to rehabilitation and in-hospital death compared to men, but this was explained by older age,

hypertension history, presence of DCI and hydrocephalus. Better management of behavioural risk factors and neurological complications could overall improve the outcomes.

Chapter 5: Adherence to evidence-based processes of care reduces one-year mortality after Aneurysmal Subarachnoid haemorrhage (aSAH)

5.1 Preface

At the time of submission, the contents of this paper were submitted to the *International Journal of Stroke*.

Rehman S, Chandra RV, Lai L, Asadi H, Dubey A, Froelich J, Thani N, Nichols L, Blizzard L, Smith K, Thrift AG, Stirling C, Callisaya ML, Breslin M, Reeves MJ, Gall S.

5.2 Abstract

Background: There is limited evidence on the provision of processes of care and survival after aneurysmal subarachnoid haemorrhage (aSAH). There are sex differences in aSAH incidence but whether these extend to care or outcomes is unknown.

Aims: We aimed to examine sex differences in (1) longer term survival and (2) adherence to evidence-based care after aSAH.

Methods: In a retrospective cohort (2010-2016) of all aSAH cases across two comprehensive Australian cerebrovascular centres, we documented 3 indicators of evidence-based aSAH care: (1) antihypertensives before aneurysm treatment, (2) nimodipine, and (3) aneurysm treatment (coiling/clipping). We defined 'optimal care' as receiving all eligible processes of care. Outcomes included discharge destination from medical records and survival at 1 year from data linkage. We analysed (1) sex differences in the risk of 1-year mortality and causes of death after aSAH; (2) the proportion of patients receiving processes of care including by sex, and (3) associations between processes of care with 1-year mortality using cox-proportional hazard model and discharge destination using log-binomial regression adjusting for sex, age, severity, and comorbidities.

Results: Among 549 patients (69% women), 59% were managed according to the guidelines, with no sex differences. Individual care indicators were associated with a lower 1-year mortality but not discharge destination. Optimal care reduced mortality at 1 year in univariable (HR 0.24 95% CI 0.17-0.35) and multivariable (HR 0.51 95% CI 0.34-0.77) analyses independent of sex, age, severity, comorbidities, and hospital network.

Conclusion: There were no differences in the provision of evidence-based care for people with aSAH by sex. Adherence to processes of care reduced 1-year mortality after aSAH. Many patients with aSAH do not receive evidence-based care and this must be addressed to improve outcomes.

5.3   Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is a rare type of stroke with poor outcomes. Approximately 25% of patients die before reaching hospital[5] and about 50% die within 6 months.[224] While there is a greater incidence of aSAH in women than men,[43] it is unclear whether this sex difference extends to processes of care or long-term survival. Sex differences in care and outcome for people with stroke may exist due to patient-level factors, such as age or comorbidities, but could also reflect gender bias in the provision of care.[27] Understanding if such differences exist, and if they do what might explain them, is important for ensuring equitable outcomes for all people with aSAH.

Clinical guidelines for the diagnosis and treatment of aSAH provide recommendations for management that are associated with better outcomes.[119, 120] European and American guidelines recommend imaging including non-contrast head computed tomography (CT)[121] scan for diagnosis of aSAH, and computed tomography angiography (CTA) and/or digital subtraction angiography (DSA) for aneurysm detection. Following confirmation, guidelines recommend (1) use of antihypertensives in the emergency department (ED) to reduce aneurysm rebleeding; (2) administration of nimodipine to prevent delayed ischaemia and improve outcomes;[5] and (3) clipping or coiling to treat the ruptured aneurysm.[124] There is a large and growing body of evidence showing that adherence to treatment guidelines is associated with better outcomes in ischaemic stroke.[225] However, it is unclear whether the benefits of adhering to guidelines also hold for aSAH. Others have observed sex differences in the receipt of evidence-based care in ischaemic stroke[125] but none have examined this for aSAH.[127]

Findings are inconsistent regarding sex differences in long-term mortality following aSAH. In the International Subarachnoid Aneurysm Trial (ISAT) standardised mortality ratios (SMR) were somewhat higher for women (1.65 95% CI 1.32-1.98) than men (1.46 95% CI 1.09-1.83) at 1 year.[75] Similarly, a greater SMR was reported for women (2.0 95% CI 1.6-2.6) than men (1.3 95% CI 0.9-1.8) in 752 aSAH patients in the Netherlands between 1985 to 2001.[82] There are also inconsistencies reported in sex differences in the causes of death following aSAH and determination of sex differences was not been the main purpose of these investigations.[82, 224] None of these authors examined associations between processes of care in aSAH and long-term mortality. A deeper understanding of sex differences in the long-term survival of aSAH, considering the quality of care, will help in targeting strategies to improve survival.

We examined (1) sex differences in 1-year mortality after aSAH including causes of death; (2) adherence to recommended processes of care after aSAH including differences by sex, and (3) whether adherence to recommended guidelines was associated with 1-year survival and discharge destination after aSAH including if these differed by sex.

5.4   Methods

This was a retrospective cohort study of all patients diagnosed with aSAH across two large public healthcare networks (Tasmania, population ~500,000 and South-east Victoria, population ~1.2 million) in Australia between 2010-2016. The study was approved by the Health and Medical Human Research Ethics Committees in Victoria (RES-18-0000-036A) and Tasmania (H0014563) with a waiver of consent. Multiple overlapping sources were used to identify the cases including admission, discharge and ward lists for the emergency, neurosurgical and radiology departments across the tertiary centres and referring hospitals. A combination of International Classification of Diseases 10 codes (160.0-160.9, 167.1 and 169.0), as either a primary or secondary diagnosis, and keyword searches were used to ascertain potential cases. A standardised abstraction form using data from radiology, pathology, and surgical reports, as well as discharge letters, were used to confirm first-ever aSAH. Potential cases were coded by one researcher in each site, and a neurosurgeon or neuro-interventional radiologist resolved any discrepancies in diagnosis.

5.4.1   Measurement of study factors

We examined 3 indicators as evidence-based best practice measures following current clinical guidelines.[119, 120] Indicator 1 was the administration of antihypertensives as recommended in US guidelines when systolic blood pressure (SBP) is ≥160mmHg[119] and in European guidelines when SBP is >180mmHg.[120] We present data for the 160mmHg SBP cut-off [226] in the main analysis and SBP>180mmHg in a sensitivity analysis. Data on receipt of antihypertensives including the time of administration before aneurysm treatment was extracted from the emergency department (ED) records along with the first reading of SBP on arrival at the hospital. We classified patients into four groups according to use of antihypertensive and their recorded systolic blood pressure (SBP) using the cut-off of ≥160mmHg (>180mmHg as an alternative cut-off) : (1) systolic blood pressure (SBP) <160mmHg in those treated with antihypertensive agents, (2) systolic blood pressure (SBP) <160mmHg in those not treated with antihypertensive agents, (3) systolic blood pressure (SBP) ≥160mmHg in those treated with antihypertensive agents, (4) systolic blood pressure (SBP) ≥160mmHg in those not treated with

antihypertensive agents. Indicator 2 was the receipt of nimodipine extracted from medical records, emergency department records, and post-operative notes. Indicator 3 was coiling or clipping to treat aneurysm including the time of treatment when ruptured aneurysm was located on neuroimaging.

Although the guidelines do not specify time frames, we examined the timing of receipt of nimodipine (within 24 hours compared to >24 hours or not treated), antihypertensive agents (within 24 hours compared to >24 hours or not treated) and aneurysm treatment (treated <72 hours compared to treated >72 hours or not treated) in sensitivity analyses. The information was extracted from surgery and discharge notes and, imaging details. Type of management (e.g. 'active aSAH care' or 'active comfort care' including only those with these orders before aneurysm treatment) was also examined as an indicator but not as part of 'optimal care' (see below).

The proportion of patients receiving 0, 1, 2, or 3 processes of care was calculated, and also the proportion receiving 'optimal care' (i.e. receiving all eligible processes of care) compared to those receiving fewer processes of care in line with previous studies of ischaemic stroke.[227]

Covariates included variables that were known to be strong predictors of the outcome,[228, 229] including age, World Federation of Neurological Surgeons (WFNS) score (I-V, higher=more severe), Modified Fisher scale (0-4, higher=more severe) and Charlson comorbidity index (0, 1 or 2, >2) and delayed cerebral ischaemia (DCI) using National Institutes of Neurological Disorders and Stroke definition (NINDS).[108]

World Federation of Neurological Surgeons (WFNS) score (I-V)[114] and Modified Fisher scale (0-4)[230] were assessed on admission and by non-contrast CT scan respectively. These severity scores are used to determine the prognosis of the disease. Charlson comorbidity index was categorized according to the number of comorbidities (0, 1 or 2, >2).[231]

A potentially important covariate that might influence provision of evidence-based care, as well as survival, was whether the person was actively managed on admission to hospital or whether they provide with active comfort care (e.g. active palliative care). Information on the type of management (e.g. 'active aSAH care' or 'active comfort care') were extracted from medical records. Patients who were placed on active comfort care after aneurysm treatment were included in the 'active' management group. The methods for dealing with this covariate in analyses is described below in the 'statistical analysis' section.

5.4.2 Outcome

The primary outcome was 1-year survival after aSAH, which was obtained by data linkage to the National Death Index (NDI). Underlying causes of death were based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. We collapsed causes of death into four categories: (1) SAH, (2) other cerebrovascular events, e.g. intracerebral haemorrhage (ICH) and ischaemic stroke (IS), (3) cardiovascular diseases, e.g. ischaemic heart disease (IHD), and (4) other causes, e.g. infection, cancer, or respiratory diseases. We calculated days from diagnosis to death up to 1 year. Patients who did not die up to 1 year were censored. As a secondary outcome, we examined discharge destination (home vs rehabilitation in survivors) after acute hospital admission.[232]

5.4.3 Statistical analysis

We examined sex differences in characteristics of patients, discharge destination, survival including causes of death and processes of care using Pearson's chi-square for categorical variables and t-test for continuous variables. Competing-risks regression[233] was used to analyse the specific hazard ratio (sHR) in women compared to men for causes of death at 1 year.

For processes of care, log-binomial regression was used to examine the likelihood of receiving each evidence-based processes of care (prevalence ratios ± 95% CI) with consideration of covariates including sex, age, WFNS, modified Fisher scale, and Charlson comorbidity index). Analyses were repeated using alternative indicators including the timing of each process of care. We also ran these analyses restricted to those that were actively managed.

We used a Cox proportional hazard model to estimate the univariable hazard ratio (HR ± 95% confidence interval [CI]) of the primary outcome of 1-year mortality by study factors including sex, processes of care (including optimal care), WFNS, modified Fisher scale, Charlson comorbidity index, and delayed cerebral ischaemia (DCI) with purposeful model building used to select covariates for models including each process of care and optimal care. Separate regression models predicting survival were run for each process of care indicator and optimal care adjusted for covariates.

Log-binomial regression was used to estimate the relative risk (RR ± 95% confidence interval [CI]) of the secondary outcome of discharge to rehabilitation compared to home among survivors including sex, optimal care, processes of care, age, WFNS, modified Fisher scale, and Charlson comorbidity index as covariates using purposeful model building, in the models

including each process of care and optimal care. Separate regression models predicting discharge destination were run for each process of care indicator and optimal care adjusted for covariates.

For both outcomes, we explored interactions between covariates and processes of care using product terms in the final multivariable models. We also explored, in detail, the role of management type (active aSAH management/care vs active comfort care) in associations between processes of care and outcomes. This included by adjusting for management type in multivariable regression models, as well as analyses restricted to those that were actively managed only.

Sensitivity analyses were performed including re-running all regression models with alternative SBP category (>180mmHg cut off), and timing of receipt of antihypertensives, nimodipine and clipping/coiling, and 'optimal care' was re-calculated with these alternative indicator definitions.

The analysis was performed in statistical software Stata 16 (StataCorp LLC, Texas, USA) and two-sided $P<0.05$ was considered statistically significant.

5.5 Results

We identified 549 patients with aSAH, with a median age of 55 (46-67) years (**Table 5-1**). Women were over-represented (69% of cases) and were older than men (median age 56 vs 54). A large proportion of patients had a favourable grade of WFNS (WFNS I, 44%) on presentation and most had a severe grade of haemorrhage recorded on CT scan (modified Fished score 4, 56%). The Charlson comorbidity score and active comfort care did not differ between the sexes.

5.5.1 Processes of care

Among individual processes of care, 85% received nimodipine and 85% received aneurysm treatment (**Table 5-2** and **Table 5-3**). Only 31% of the eligible cohort received antihypertensive agents in the ED. Optimal care was received by 59% of all patients. There were no sex differences in individual processes of care or optimal care. Most received nimodipine and antihypertensives within one day and aneurysm treatment within 72 hours with no difference by sex (**Table 5-4**). Optimal care was received by 64% of those actively managed and none on active comfort care (**Table 5-5**). There was a lesser prevalence of receiving nimodipine, aneurysm treatment and optimal care in patients with poor-grade aSAH and among those who were put on active comfort care , but there were no differences by sex (**Table 5-6**).

5.5.2 Mortality up to 1 year

In our cohort, 27% died within 1 year of onset of aSAH (**Table 5-7**). The median days of survival and death rate up to 1 year were similar in both sexes (27% men vs 26% women) (p=0.87, **Table 5-7**). Almost all patients put on active comfort care subsequently died.

5.5.3 Cause-specific mortality

Death from aSAH was the most common cause of death (71%) within 1 year. Causes of death were similar for women and men (**Table 5-7**). In women, the risk of dying from the SAH was the same as in men (sHR 1.06 95% CI 0.71-1.59, p=0.76) when adjusted for age and comorbidities in competing risk analysis (**Table 5-8**).

Table 5-1 Characteristics of aSAH in the whole cohort by sex

Variable	Total* N=549		Men* N=170		Women* N=379		P-value
	N	(%)	N	%	N	(%)	
Age Median (IQR 1-3)	55	(46-67)	54	(45-64)	56	(47-70)	0.04
Charlson comorbidity score							0.13
0	396	(72)	132	(77)	264	(70)	
1 or 2	114	(21)	27	(16)	87	(23)	
>2	39	(7)	11	(6)	28	(7)	
WFNS							0.53
I	246	(45)	85	(50)	161	(42)	
II	97	(18)	27	(16)	70	(18)	
III	25	(4)	6	(3)	19	(5)	
IV	47	(9)	12	(7)	35	(9)	
V	124	(23)	38	(22)	86	(23)	
Missing	10	(2)	2	(1)	8	(2)	
Modified Fisher score							0.56
0	6	(1)	1	(1)	5	(1)	
1	49	(8)	17	(10)	32	(8)	
2	18	(3)	8	(4)	10	(3)	
3	110	(20)	37	(22)	73	(19)	
4	310	(56)	92	(54)	218	(58)	
Missing	56	(10)	15	(9)	41	(11)	
Hospital network							0.93
Hospital 1 (Victoria)	334	(61)	103	(61)	231	(61)	
Hospital 2 (Tasmania)	215	(39)	67	(39)	148	(39)	
Ventriculostomy before aneurysm treatment							0.11
No	299	(54)	102	(60)	197	(52)	
Yes	246	(45)	68	(40)	178	(47)	
Missing	4	(1)	0	(0)	4	(1)	
Delayed cerebral ischaemia (DCI)							0.003
No	368	(67)	128	(75)	240	(63)	
Yes	153	(28)	33	(19)	120	(32)	
Missing	28	(5)	9	(5)	19	(5)	
Active Comfort care							0.20
No	488	(89)	148	(87)	340	(89)	
Yes	57	(10)	22	(13)	35	(9)	

Missing	4	(1)	0	(0)	4	(1)

*Number and (%), unless otherwise indicated, WFNS World Federation of Neurological Surgeons grading

Table 5-2 Processes of care in aSAH in the whole cohort and, in men and women

Variable	Total*		Men*		Women*		P-value
	N	(%)	N	(%)	N	(%)	
Nimodipine							0.85
No	81	(14)	26	(15)	55	(14)	
Yes	464	(85)	144	(85)	320	(84)	
Missing	4	(1)	0	(0)	4	(1)	
Aneurysm treated							0.40
No	80	(15)	28	(16)	52	(14)	
Yes	468	(85)	142	(84)	326	(86)	
Missing	1	(0.1)	0	(0)	1	(0.2)	
Antihypertensive							0.85
SBP<160/No antihypertensive	270	(49)	84	(49)	186	(49)	
SBP≥160/No antihypertensive	143	(26)	42	(25)	101	(27)	
SBP<160/Yes antihypertensive	43	(8)	13	(8)	30	(8)	
SBP≥160/Yes antihypertensive	65	(12)	23	(13)	42	(11)	
Missing	28	(5)	8	(5)	20	(5)	
Number of evidence-based processes of care							0.82
0	31	(6)	11	(6)	20	(5)	
1	47	(8)	14	(8)	33	(8)	
2	148	(30)	42	(25)	106	(28)	
3	323	(59)	103	(60)	220	(58)	
Optimal care							0.57
Did not receive ≥1 treatment	226	(41)	67	(39)	159	(42)	
Received all treatments	323	(59)	103	(61)	220	(58)	

*Number and (%), unless otherwise indicated

Table 5-3 Individual diagnostic processes in men and women

Variable	Total* N=549		Men* N=170		Women* N=379		P-value
	N	(%)	N	(%)	N	(%)	
CT (any type)							0.94
No	10	(2)	3	(2)	7	(2)	
Yes	537	(97.5)	167	(98)	370	(97)	
Missing	2	(0.3)	0	(0)	2	(0.5)	
Non-contrast CT							0.59
No	71	(13)	24	(14)	47	(12)	
Yes	470	(85)	144	(84)	326	(86)	
Missing	8	(1)	2	(1)	6	(1.5)	
CT Angiography							0.32
No	90	(16)	24	(14)	66	(17)	
Yes	451	(82)	144	(84)	307	(81)	
Missing	8	(1)	2	(1)	6	(2)	
Digital Subtraction Angiography							0.13
No	135	(25)	49	(29)	86	(23)	
Yes	412	(75)	121	(71)	291	(76)	
Missing	2	(0.3)	0	(0)	2	(0.5)	
Magnetic Resonance Imaging							0.51
No	515	(94)	159	(94)	356	(94)	
Yes	30	(5)	11	(6)	19	(5)	
Missing	4	(1)	0	(0)	4	(1)	
Lumbar Puncture							0.16
No	511	(93)	157	(92)	354	(93)	
Yes	25	(5)	11	(7)	14	(4)	
Missing	13	(2)	2	(1)	11	(3)	

*Number and (%), unless otherwise indicated

Table 5-4 Time delays in receipt of medication and aneurysm treatment and optimal care in men and women in alternative classifications

Variable	Total*		Men*		Women*		P-value
	N	(%)	N	(%)	N	(%)	
Nimodipine							0.89
Within 24 hours	278	(60)	84	(58)	194	(58)	
After 24 hours							
7 days	150	(32)	48	(33)	102	(33)	
14 days	20	(4)	8	(6)	12	(5)	
21 days	5	(1)	2	(1)	3	(1)	
>21 days	6	(1)	2	(1)	4	(1)	
Missing	5	(1)	0	(0)	5	(17)	
Nimodipine							0.51
Not treated/> 24 hours	262	(48)	86	(51)	176	(46)	
≤24 hours	278	(51)	84	(49)	194	(51)	
Missing	9	(1)	0	(0)	9	(2)	
Antihypertensives if SBP≥160							0.24
Within 24 hours	56	(86)	18	(78)	38	(90)	
After 24 hours							
2 days	3	(5)	1	(4)	2	(5)	
>2 days	6	(9)	4	(17)	2	(5)	
Antihypertensives if SBP≥160							0.86
Not treated/>24 hours	152	(73)	47	(72)	105	(73)	
≤24 hours	56	(27)	18	(28)	38	(27)	
Clipping							0.74
No	367	(67)	112	(66)	255	(67)	
Yes	182	(33)	58	(34)	124	(33)	
Missing	0	(0)	0	(0)	0	(0)	
Coiling							0.48
No	259	(47)	84	(49)	175	(46)	
Yes	290	(53)	86	(51)	204	(54)	
Aneurysm treatment time							0.05
Not treated/>72 hrs	132	(24)	50	(29)	82	(22)	
≤72 hrs	409	(74)	118	(70)	291	(78)	
Antihypertensive if SBP> 180							0.27
SBP≤180/No antihypertensive	354	(64)	113	(66)	241	(63)	
SBP>180/No antihypertensive	59	(10)	13	(8)	46	(12)	
SBP≤180/Yes antihypertensive	82	(14)	25	(14)	57	(15)	
SBP>180/Yes antihypertensive	26	(5)	11	(6)	15	(4)	

Missing	28	(5)	8	(4)	20	(5)	
Optimal care*							0.60
No	366	(67)	116	(68)	250	(66)	
Yes	183	(33)	54	(32)	129	(34)	
Optimal care**							0.51
No	159	(29)	46	(27)	113	(30)	
Yes	390	(71)	124	(73)	266	(70)	

*optimal care when aneurysm treatment performed within 72 hours, nimodipine and antihypertensives within 24 hours

**optimal care when SBP>180mmHg as cut-off

Table 5-5 Patient characteristics and processes of care according to type of management (active comfort care vs actively managed with active aSAH care)

	Active comfort care* N=57		Actively managed* N=488		P-value
	N	**(%)**	**N**	**(%)**	
Patient characteristics					
Age Median (IQR1-IQR3)	71	(55-80)	54	(45-64)	<0.001
WFNS					<0.001
I	8	(14)	237	(48)	
II	3	(5)	93	(19)	
III	4	(7)	21	(4)	
IV	4	(7)	43	(8)	
V	38	(36)	85	(17)	
Missing	0	(0)	9	(1)	
Modified Fisher score					<0.001
0	0	(0)	6	(1)	
1	0	(0)	48	(9)	
2	0	(0)	18	(3)	
3	3	(5)	107	(21)	
4	45	(79)	263	(54)	
Missing	9	(15)	46	(9)	
Charlson comorbidity score					0.004
0	31	(54)	362	(74)	
1 or 2	21	(36)	92	(19)	
>2	5	(8)	34	(6)	
Processes of care					
Nimodipine					<0.001
No	41	(72)	37	(4)	
Yes	16	(28)	447	(96)	
Missing	0	(0)			
Aneurysm treated					<0.001
No	57	(48)	20	(4)	
Yes			568	(94)	
Missing	0	(0)	1	(0.23)	
Antihypertensive					0.02
SBP<160/No antihypertensive	27	(47)	243	(50)	
SBP≥160/No antihypertensive	22	(38)	121	(24)	
SBP<160/Yes antihypertensive			43	(9)	
SBP≥160/Yes antihypertensive	5	(8)	59	(12)	
Missing	3	(5)	22	(4)	
Optimal care					<0.001
No	57	(100)	165	(33)	
Yes	0	(0)	323	(64)	

Secondary outcome
Discharge Destination <0.001

Death	57	(100)	83	(17)
Home	0	(0)	203	(42)
Rehabilitation	0	(0)	198	(41)

*Number and (%), unless otherwise indicated, WFNS World Federation of Neurological Surgeons grading, Information on comfort care missing in N=4 participants

Table 5-6 Unadjusted and adjusted prevalence ratios of processes of care and optimal care according to sex, age, Charlson comorbidity index, severity, and management type

Care processes	Nimodipine		Antihypertensive		Aneurysm treated		Optimal care	
	Unadjusted PR (95% CI)	Adjusted* PR (95% CI)	Unadjusted PR (95% CI)	Adjusted* PR (95% CI)	Unadjusted PR (95% CI)	Adjusted* PR (95% CI)	Unadjusted PR (95% CI)	Adjusted* PR (95% CI)
Sex								
Men	Ref		Ref		Ref		Ref	
Women	1.01 (0.93-1.08)	1.02 (0.95-1.09)	0.83 (0.54-1.25)	0.85 (0.56-1.29)	1.03 (0.95-1.11)	1.04 (0.98-1.11)	0.95 (0.82-1.11)	1.04 (0.91-1.20)
Age	**0.998 (0.996-1.00)**	0.999 (0.997-1.00)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	**0.997 (0.996-0.998)**	0.998 (0.995-1.00)	0.99 (0.98-1.00)	**0.99 (0.98-1.00)**
Charlson comorbidity index								
0	Ref		Ref		Ref		Ref	
1 or 2	0.98 (0.90-1.08)	1.01 (0.93-1.09)	0.88 (0.53-1.46)	0.91 (0.53-1.56)	0.90 (0.81-1.00)	0.96 (0.89-1.05)	**0.87 (0.72-1.05)**	0.92 (0.75-1.13)
>2	1.05 (0.94-1.18)	1.09 (0.99-1.04)	0.76 (0.34-1.68)	0.98 (0.46-2.08)	0.96 (0.84-1.11)	1.05 (0.93-1.19)	0.83 (0.61-1.15)	0.95 (0.73-1.24)
WFNS (I-V)	**0.93 (0.91-0.96)**	**0.95 (0.93-0.98)**	0.85 (0.75-0.97)	**0.80 (0.69-0.92)**	**0.92 (0.93-0.95)**	**0.95 (0.93-0.97)**	**0.84 (0.80-0.90)**	**0.87 (0.83-0.93)**
Modified Fisher score (0-4)	**0.96 (0.94-0.98)**	1.01 (0.99-1.04)	0.93 (0.78-1.12)	1.07 (0.87-1.31)	**0.95 (0.94-0.96)**	1.01 (0.99-1.03)	0.94 (0.89-1.00)	1.07 (0.99-1.16)
Management type								
Active aSAH care	Ref		Ref		Ref		Ref	
Active Comfort care	**0.64 (0.55-0.74)**	**0.69 (0.60-0.80)**	0.84 (0.52-1.35)	1.08 (0.64-1.84)	**0.54 (0.45-0.65)**	**0.62 (0.52-0.74)**	**0.41 (0.31-0.55)**	**0.57 (0.42-0.78)**

*Adjusted for hospital network, WFNS World Federation of Neurological Surgeons grading

Table 5-7 Mortality in men and women and causes of death up to 1 year after aSAH

Variables of mortality	Total*		Men*		Women*		P-value
	N	(%)	N	%	N	(%)	
Cohort deceased by 1 year	146	(26.5)	46	(27)	100	(26.3)	0.87
Median days till death (range)	4	0-107	4	0-93	4	0-107	
Mean(±SD) days till death	11.86	18.06	10.73	15.46	12.39	19.19	
Causes of death							
SAH	104	(71)	32	(70)	72	(72)	0.96
Other cerebrovascular events	24	(16)	7	(15)	17	(17)	
Cardiovascular events	5	(3)	2	(4)	3	(3)	
Other causes	11	(8)	3	(6)	8	(8)	
Missing	2	(1)	2	(4)	0	(0)	

*Number and (%), unless otherwise indicated

Table 5-8 Specific Hazard Ratio in women compared to men for cause of death up to 1 year

Cause of death	Unadjusted sHR (95%CI)	Adjusted sHR (95%CI)	Covariates adjusted
Subarachnoid haemorrhage	1.03 (0.69-1.53)	1.06 (0.71-1.59)	Age and Charlson comorbidity index
Other cerebrovascular events	1.11 (0.46-2.65)	1.11 (0.47-2.63)	Age and Charlson comorbidity index
Cardiovascular events	0.69 (0.12-4.12)	0.68 (0.13-3.47)	Age and Charlson comorbidity index
Other conditions like infection, respiratory diseases, cancer	1.19 (0.31-4.49)	1.16 (0.30-4.46)	Age and Charlson comorbidity index

5.5.4 Predictors of outcomes after aSAH including sex, processes of care and covariates

For the primary outcome of mortality to 1 year, in univariable analysis among all cases (**Table 5-9**) there was an increased hazard ratio for mortality associated with age, greater number of comorbidities, WFNS score and modified Fisher scale but not sex. Receiving each care indicator, except antihypertensives and optimal care was associated with a lower likelihood of death. In multivariable analyses adjusted for sex, age, severity scores, comorbidities, DCI, aneurysm treatment, nimodipine, and optimal care all remained associated with a reduced risk of death at 1 year. We did not find an interaction between processes of care or optimal care with sex, age, severity grade or management type suggesting these did not modify the effect of evidence-based care on survival. However, given the large influence of being placed on comfort measures on the care provided and on outcome, we repeated analyses restricted to actively managed patients only (n=488). In this group, receipt of nimodipine and aneurysm treatment were associated with longer survival (**Table 5-10**). We also performed analysis adjusting for management type. Aneurysm treatment and nimodipine, but not optimal care, were associated with a reduced risk of death at 1 year with no difference by sex (**Table 5-11**)

For the secondary outcome of discharge destination, more patients discharged to rehabilitation and home received optimal care (rehabilitation 63%, home 76%) compared to those who died (30%, p=<0.001,**Table 5-12**). There were no interactions between covariates, including sex, with processes of care and discharge destination. As all patients who were not actively managed died, we did not repeat analyses for association between processes of care and discharge destination by management type or with adjustment for management type because this groups included survivors only.

Table 5-9 Hazard ratio of mortality at 1 year associated with individual processes of care and optimal care adjusted for covariates

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Female sex	0.97 (0.68-1.37)	0.74 (0.50-1.11)	0.92 (0.61-1.37)	0.69 (0.38-1.24)	0.75 (0.50-1.13)
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	**0.14** (**0.10-0.20**)	**0.19** (**0.12-0.32**)			
Aneurysm treated					
No	Ref		Ref		
Yes	**0.07** (**0.05-0.10**)		**0.19** (**0.06-0.18**)		
Antihypertensive					
No	Ref			Ref	
Yes	0.64 (0.37-1.10)			1.20 (0.65-2.21)	
Optimal care					
No	Ref				Ref
Yes	**0.24** (**0.17-0.35**)				**0.51** (**0.34-0.77**)
Covariates					
Age	**1.04** (**1.03-1.05**)	**1.04** (**1.02-1.05**)	**1.02** (**1.00-1.03**)	1.05 (1.03-1.08)	**1.04** (**1.02-1.06**)
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	**1.70** (**1.17-2.46**)	1.50 (0.93-2.42)	1.28 (0.79-2.05)	1.36 (0.68-2.70)	1.25 (0.78-1.99)
>2	**1.91**	**2.30**	**1.90**	1.73	1.66

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
	(1.12-3.26)	(1.24-2.48)	(1.02-3.53)	(0.84-3.56)	(0.75-2.97)
WFNS	1.72	1.60	1.51	1.92	1.70
	(1.54-1.91)	(140-1.84)	(1.31-1.73)	(1.56-2.36)	(1.49-1.95)
Modified Fisher scale	2.60	1.52	1.43	1.39	1.54
	(1.80-3.75)	(1.07-2.14)	(1.00-2.03)	(0.92-2.10)	(1.10-2.16)
Delayed cerebral ischaemia (DCI)	0.63	0.55	0.79	0.35	0.39
	(0.42-0.95)	(0.33-0.92)	(0.46-1.33)	(0.19-0.65)	(0.24-0.62)

*Adjusted for year and hospital network, WFNS World Federation of Neurological Surgeons grading

Table 5-10 Hazard ratio of mortality at 1 year associated with individual processes of care and optimal care in actively managed patients

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Female sex	1.17 (0.73-1.88)	0.83 (0.48-1.41)	0.94 (0.56-1.6)	0.97 (0.47-2.01)	0.85 (0.50-1.45)
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	**0.28** **(0.16-0.20)**	**0.19** **(0.09-0.39)**			
Aneurysm treated					
No	Ref		Ref		
Yes	**0.20** **(0.10-0.39)**		**0.07** **(0.02-0.17)**		
Antihypertensive					
No	Ref			Ref	
Yes	0.75 (0.39-1.42)			1.33 (0.66-2.69)	
Optimal care					
No	Ref				Ref
Yes	**0.50** **(0.33-0.76)**				0.81 (0.51-1.33)
Covariates					
Age	**1.03** **(1.02-1.05)**	**1.04** **(1.02-1.06)**	**1.04** **(1.02-1.06)**	1.02 (0.99-1.05)	**1.04** **(1.02-1.06)**
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	1.38 (0.83-2.30)	1.28 (0.69-2.35)	1.15 (0.63-2.08)	1.24 (0.51-3.01)	1.13 (0.62-2.07)

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
>2	**2.20** **(1.15-4.21)**	**2.15** **(1.06-4.36)**	**2.05** **(1.02--4.11)**	2.23 (0.98-5.07)	1.88 (0.93-3.80)
WFNS	**1.64** **(1.44-1.87)**	**1.64** **(1.39-1.9)**	**1.63** **(1.39-1.91)**	**1.78** **(1.39-2.29)**	**1.70** **(1.45-2.00)**
Modified Fisher scale	**2.12** **(1.45-3.11)**	**1.44** **(1.00-2.06)**	**1.47** **(1.01-2.14)**	1.26 (0.80-1.97)	**1.43** **(1.00-2.03)**
Delayed cerebral ischaemia (DCI)	1.12 (0.71-1.77)	0.66 (0.37-1.18)	0.61 (0.34-1.08)	**0.42** **(0.19-0.92)**	**0.51** **(0.29-0.90)**

*Adjusted for year and hospital network, WFNS World Federation of Neurological Surgeons grading

Table 5-11 Hazard ratio of mortality at 1 year associated with individual processes of care and optimal care including additional adjustment for type of management

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Female sex	0.97 (0.68-1.37)	1.05 (0.69-1.60)	1.07 (0.70-1.62)	1.05 (0.56-1.97)	1.03 (0.67-1.57)
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	**0.14** **(0.10-0.20)**	**0.28** **(0.16-0.48)**			
Aneurysm secured					
No	Ref		Ref		
Yes	**0.07** **(0.05-0.10)**		**0.08** **(0.03-0.19)**		
Antihypertensive					
No	Ref			Ref	
Yes	0.64 (0.37-1.10)			1.36 (0.72-2.55)	
Optimal care					
No	Ref				Ref
Yes	**0.24** **(0.17-0.35)**				0.79 (0.49-1.27)
Management type					
Active aSAH care	Ref	Ref	Ref	Ref	Ref
Active comfort care	**25.34** **(16.88-38.03)**	**5.37** **(2.83-10.19-)**	**1.14** **(0.51-2.58)**	**8.97** **(3.45-23.35)**	**8.24** **(4.32-15.71)**
Covariates					
Age	**1.04** **(1.03-1.05)**	**1.03** **(1.01-1.04)**	**1.02** **(1.01-1.04)**	1.02 (1.00-1.05)	**1.02** **(1.01-1.04)**

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	**1.70** (1.17-2.46)	1.22 (0.74-1.99)	1.04 (0.64-1.70)	1.03 (0.50-2.14)	1.05 (0.64-1.71)
>2	**1.91** (1.12-3.26)	**2.01** (1.04-3.75)	1.67 (0.90-3.11)	1.73 (0.82-3.65)	1.68 (0.90-3.15)
WFNS	**1.72** (1.54-1.91)	**1.57** (1.37-1.80)	**1.56** (1.36-1.79)	**1.75** (1.42-2.16)	**1.58** (1.37-1.81)
Fisher scale	**2.60** (1.80-3.75)	1.38 (0.98-1.94)	1.42 (1.00-2.02)	1.26 (0.83-1.93)	1.38 (0.99-1.94)
Delayed cerebral ischaemia (DCI)	**0.63** (0.42-0.95)	0.70 (0.42-1.17)	0.79 (0.47-1.33)	0.60 (0.29-1.23)	0.66 (0.39-1.09)

*Adjusted for year and hospital network, WFNS World Federation of Neurological Surgeons grading

Table 5-12 Comparison of acute outcome in patients receiving individual processes of care and optimal care

Processes of care	Death (N=142)		Rehabilitation (N=200)		Home (N=203)		P-value
	N	%	N	%	N	%	
Nimodipine							<0.001
No	59	(42)	11	(5)	11	(5)	
Yes	83	(58)	189	(95)	192	(95)	
Missing	0	(0)	0	(0)	0	(0)	
Antihypertensives							0.24
No	56	(77)	59	(73)	35	(62)	
Yes	17	(23)	21	(26)	20	(36)	
Missing	0	(0)	1	(1)	0	(0)	
Aneurysm treatment							<0.001
No	69	(49)	4	(2)	7	(3)	
Yes	73	(51)	195	(97)	196	(96)	
Missing	0	(0)	1	(0.5)	0	(0)	
Optimal care							<0.001
No	100	(70)	73	(37)	49	(24)	
Yes	42	(30)	127	(63)	154	(76)	

5.5.4.1 Sensitivity analyses with alternative indicators of processes of care

In the cohort with SBP>180mmHg, receipt of antihypertensive was not associated with better survival. In the analysis of optimal care using the alternative indicator of SBP, the results were similar for 1-year survival (**Table 5-13**). Refining the process of care for receipt of nimodipine within 24 hours and treating aneurysm to within 72 hours was associated with longer survival (**Table 5-13**). Among survivors, receipt of nimodipine, aneurysm treatment and optimal care was relatively greater for those discharged home with a larger difference seen when the time to receiving processes of care was taken into account (**Table 5-14**, **Table 5-15** and **Table 5-16**).

Table 5-13 Hazard ratio of mortality at 1 year associated with the alternative classification of individual processes of care and optimal care

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Female sex	0.97 (0.68-1.37)	0.71 (0.49-1.07)	0.95 (0.62-1.44)	0.70 (0.39-1.24)	1.40 (0.51-3.80)	0.73 (0.48-1.09)	**0.78 (0.52-1.17)**
Processes of care							
Nimodipine							
Received after 24 hrs	Ref	Ref					
Received within 24 hrs	**0.63 (0.45-0.88)**	**0.61 (0.42-0.89)**					
Aneurysm treated							
Not treated/>72 hrs	Ref		Ref				
≤72 hrs	**0.19 (0.14-0.27)**		**0.20 (0.13-0.31)**				
Antihypertensive							
Received after 24 hrs	Ref			Ref			
Received within 24 hrs	0.73 (0.42-1.26)			1.33 (0.72-2.45)			
Antihypertensive >180mmHg							
No	**Ref**				Ref		
Yes	0.69 (0.32-1.49)				1.63 (0.58-4.52)		
Optimal care**							
No	Ref					Ref	
Yes	**0.49 (0.33-0.73)**					0.68 (0.44-1.04)	
Optimal care***							
No	Ref						Ref
Yes	**0.20 (0.14-0.27)**						**0.41 (0.27-0.61)**
Covariates							
Age	**1.04 (1.03-1.05)**	**1.04 (1.03-1.06)**	**1.02 (1.00-1.04)**	**1.05 (1.03-1.08)**	**1.04 (1.00-1.08)**	**1.04 (1.03-1.06)**	**1.04 (1.02-1.05)**

Mortality at 1 year	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Charlson comorbidity index							
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1 or 2	**1.70** (1.17-2.46)	1.26 (0.79-2.03)	1.13 (0.70-1.83)	1.35 (0.68-2.69)	1.02 (0.30-3.46)	1.16 (0.73-1.84)	1.24 (0.78-1.98)
>2	**1.91** (1.12-3.26)	1.86 (0.99-3.50)	**1.93** (1.03-3.60)	1.79 (0.87-3.68)	**3.33** (1.00-11.03)	1.79 (0.97-3.30)	**1.85** (1.00-3.04)
WFNS	**1.72** (1.54-1.91)	**1.82** (1.60-2.08)	**1.66** (1.45-1.90)	**1.92** (1.57-2.36)	**1.69** (1.24-2.30)	**1.78** (1.56-2.03)	**1.64** (1.43-1.88)
Modified Fisher scale	**2.60** (1.80-3.75)	**1.58** (1.12-2.23)	**1.85** (1.27-2.68)	1.38 (0.91-2.09)	**1.53** (0.77-3.01)	**1.55** (1.10--2.18)	**1.53** (1.10-2.13)
Delayed cerebral ischaemia (DCI)	**0.63** (0.42-0.95)	**0.32** (0.20-0.53)	**0.55** (0.34-0.89)	**0.32** (0.16-0.61)	**0.33** (0.11-0.97)	**0.36** (0.22-0.58)	**0.41** (0.26-0.66)

*Adjusted for year and hospital network, WFNS World Federation of Neurological Surgeons grading

**optimal care when aneurysm treatment performed within 72 hours, nimodipine and antihypertensives received within 24 hours

***optimal care when SBP >180mmHg is cut-off

Table 5-14 Prevalence of processes of care and optimal care in those discharged to home compared to discharged to rehabilitation as the reference category

	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Female sex	0.86 (0.70-1.05)	**1.06 (1.04-1.09)**	1.07 (0.97-1.18)	0.92 (0.65-1.31)	**1.06 (1.04-1.09)**
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	1.00 (0.65-1.54)	1.76 (0.71-4.34)			
Aneurysm secured					
No	Ref		Ref		
Yes	0.78 (0.49-1.24)		1.02 (0.48-2.20)		
Antihypertensive					
No	Ref			Ref	
Yes	1.24 (0.83-1.87)			1.16 (0.77-1.74)	
Optimal care					
No	Ref				Ref
Yes	1.11 (0.90-1.36)				1.06 (0.91-1.24)
Covariates					
Age	**0.986 (0.985-0.988)**	**0.989 (0.986-0.992)**	**0.989 (0.986-0.993)**	**0.979 (0.968-0.990)**	**0.990 (0.986-0.993)**
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	0.80 (0.61-1.06)	0.90 (0.68-1.18)	0.91 (0.68-1.20)	1.07 (0.62-1.86)	0.91 (0.70-1.20)
>2	**0.48 (0.24-0.96)**	0.53 (0.25-1.11)	0.53 (0.25-1.12)	0.57 (0.09-3.57)	0.52 (0.25-1.11)
WFNS	**0.62 (0.54-0.71)**	**0.66 (0.58-0.76)**	**0.66 (0.57-0.76)**	**0.71 (0.57-0.89)**	**0.66 (0.58-0.76)**
Modified Fisher scale	**0.81 (0.77-0.86)**	**0.92 (0.90-0.94)**	0.92 (0.87-0.98)	0.91 (0.79-1.03)	**0.92 (0.90-0.95)**

WFNS World Federation of Neurological Surgeons grading

Table 5-15 Prevalence of processes of care and optimal care in those discharged to home compared to discharged to rehabilitation as the reference category in actively managed patients

	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Female sex	0.87 (0.71-1.06)	**1.06 (1.04-1.09)**	1.07 (0.97-1.18)	0.92 (0.65-1.31)	**1.06 (1.04-1.09)**
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	0.96 (0.63-1.46)	1.38 (0.57-3.36)			
Aneurysm secured					
No	Ref		Ref		
Yes	0.71 (0.47-1.08)		0.97 (0.47-1.97)		
Antihypertensive					
No	Ref			Ref	
Yes	1.27 (0.85-1.91)			1.17 (0.78-1.76)	
Optimal care					
No	Ref				Ref
Yes	1.34 (1.05-1.70)				1.16 (0.93-1.45)
Covariates					
Age	**0.986 (0.985-0.988)**	**0.989 (0.986-0.992)**	**0.989 (0.986-0.993)**	**0.979 (0.968-0.990)**	**0.990 (0.987-0.993)**
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	0.81 (0.61-1.07)	0.91 (0.69-1.19)	0.91 (0.69-1.20)	1.09 (0.63-1.8)	0.92 (0.70-1.20)
>2	**0.48 (0.24-0.96)**	0.53 (0.25-1.11)	0.53 (0.25-1.12)	0.57 (0.09-3.574)	0.52 (0.25-1.08)
WFNS	**0.62 (0.54-0.71)**	**0.66 (0.58-0.76)**	**0.66 (0.57-0.76)**	**0.71 (0.57-0.89)**	**0.66 (0.58-0.76)**
Modified Fisher scale	**0.81 (0.78-0.86)**	**0.92 (0.90-0.94)**	0.92 (0.87-0.98)	0.91 (0.79-1.03)	**0.93 (0.90-0.95)**

WFNS World Federation of Neurological Surgeons grading

Table 5-16 Prevalence of processes of care and optimal care in those discharged to home compared to discharged to rehabilitation as the reference category (optimal care category with optimal time to treatment)**

	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Female sex	0.86 (0.70-1.05)	1.03 (0.92-1.48)	1.08 (0.98-1.20)	0.92 (0.67-1.28)	**1.06 (1.04-1.09)**
Processes of care					
Nimodipine					
No	Ref	Ref			
Yes	1.01 (0.83-1.23)	1.10 (0.95-1.27)			
Aneurysm secured					
No	Ref		Ref		
Yes	**0.69 (0.56-0.85**)		0.87 (0.76-1.00)		
Antihypertensive					
No	Ref			Ref	
Yes	1.29 (0.85-1.96)			1.29 (0.82-2.05)	
Optimal care					
No	Ref				Ref
Yes	1.18 (0.98-1.44)				1.18 (0.97-1.28)
Covariates					
Age	**0.986 (0.985-0.988)**	**0.990 (0.986-0.993)**	**0.989 (0.985-0.992)**	**0.980 (0.968-0.990)**	**0.991 (0.986-0.994)**
Charlson comorbidity index					
0	Ref	Ref	Ref	Ref	Ref
1 or 2	0.80 (0.61-1.06)	0.95 (0.71-1.27)	0.91 (0.70-1.20)	1.08 (0.62-1.86)	0.92 (0.69-1.23)
>2	**0.48 (0.24-0.96)**	0.53 (0.25-1.11)	0.54 (0.25-1.14)	0.65 (0.10-4.26)	0.52 (0.25-1.09)
WFNS	**0.62 (0.54-0.71)**	**0.66 (0.58-0.76)**	**0.67 (0.58-0.77)**	**0.71 (0.57-0.89)**	**0.66 (0.57-0.76)**
Modified Fisher scale	**0.81 (0.77-0.86)**	**0.94 (0.89-0.99)**	**0.93 (0.87-0.98)**	0.88 (0.75-1.03)	**0.93 (0.90-0.95)**

**optimal care when aneurysm treatment performed within 72 hours, nimodipine and antihypertensives received within 24 hours, WFNS World Federation of Neurological Surgeons grading

5.6 Discussion

To the best of our knowledge, this is the first study undertaken to examine adherence to evidence-based processes of care and association with mortality up to 1 year for patients with aSAH. We had a particular focus on whether there were sex differences in these aspects of aSAH but found no apparent differences in longer term survival, causes of death or receipt of evidence-based care between men and women. Notably, while most patients received individual processes of care per current guidelines, optimal care was received by 59% of the patients. Patients who were treated according to evidence-based processes of care had lower mortality at 1 year, but the outcome was similar in those discharged home versus those discharged to rehabilitation as a reference category.

Sex did not predict long-term survival after aSAH. Overall, 27% of patients had died within 1 year, a proportion that was similar for women and men. Among causes of death, initial bleed from aSAH was the most common with no difference between men and women. This stresses the importance of acute care for aSAH to reduce early death. Predictors of mortality in our cohort were age, presence of other comorbidities, severity and, perhaps not surprisingly, being placed in active palliative care or 'active comfort care'. Age is an established factor of mortality in SAH.[224] The risk of death and poor outcome increases in elderly patients of SAH[234] due to frailty and a higher number of comorbidities. The severity of aSAH measured through WFNS and Fisher score grading scales were also associated with 1-year mortality. These scales estimate neurological damage through neurological examination or indirectly through the extent of the haemorrhage. They are strongly associated with the outcome of the disease[235] and guide clinical decision making on treatment.[236] Others have noted that severity on admission to determine prognosis or guide decisions is flawed due to misestimation in some patients and inter-observer variability.[237] Therefore, it is possible that some patients categorized as poor grade with predicted poor prognosis did not receive evidence-based care but may have benefited from active management.[238]

The indicators for the management of aSAH selected for inclusion in this analysis were from the most recent United States and European guidelines, noting that these are both almost 10 years old.[119, 120] Our analyses highlight that there are limited indicators for the care of people with aSAH with level 1 evidence. Nimodipine, a calcium channel blocker, was not received by some patients who had a poor grade of aSAH and were provided active comfortcare. Another reason for not receiving nimodipine could be the presence of contraindications such as

hypersensitivity or hypotension,[239] symptoms that were not possible to record in our study. Nimodipine is recommended for all aSAH[119] patients to reduce the event of DCI and improve the neurological outcome[209] so lower use in poor-grade patients should be explored further. Similarly, patients with poor-grade WFNS and the elderly had their aneurysm treated less often. The decision for aneurysm treatment depends on factors like age, comorbidity, WFNS grade, or aneurysm morphology.[240] However, guidelines state that aneurysm should be secured as early as 'logistically and technically' possible with this decision independent of the grade of aSAH.[120] Few eligible patients (31%) received antihypertensive medications in the ED according to set the cut-off value of SBP in our study from the American Heart Association (AHA) guidelines.[119] This discrepancy in management of blood pressure needs to be addressed in the acute management of aSAH with further research regarding the upper limit for SBP associated with better outcomes.

Approximately 40% of patients did not receive optimal care. The population not provided with optimal care (reception of aSAH specific measures) was older, with a poor grade of aSAH deemed for active palliative treatment but there were no differences according to sex. Increased age and poor grade of aSAH have previously been shown to predict referral for active palliative treatment.[236] Some investigators have questioned not actively treating older and poor-grade aSAH patients,[238] showing evidence of a favourable outcome in such patients. Therefore, exploring ways to increase access to optimal care to all patients with aSAH irrespective of age and grade could help in improving the outcome.

Individual processes of care and optimal care improved the survival of the patients of aSAH by reducing death at 1 year without any sex differences. While there was evidence of somewhat increased discharge to home compared to rehabilitation associated with individual processes of care and optimal care, these were not statistically significant. Of note is the reduced sample size for analyses of discharge destination in survivors that may have affected our ability to detect differences, so future studies with larger samples are encouraged. There was evidence that receiving processes of care within shorter time frames enhanced the benefit of survival and discharge to home, with larger effect sizes in these analyses. DCI was associated with better survival replicating our previous findings.[232] Overall these findings are supported by improved short-term and long-term outcomes in ischaemic stroke when the uncompromised quality of care is provided.[227, 241] To reduce the gaps in evidence-based care of aSAH, strategies such as quality of care registries, audit and feedback could be implemented.[242]

It is important to highlight that 10% of patients were put on 'active comfort care', e.g. without active aSAH management, and all eventually died. In actively managed patients there was no longer a detectable effect of optimal care with this group younger with less severe stroke than the active comfort care group, which may confound associations with outcomes. The patients placed on active comfort care were older, had poor-grade SAH and had more comorbidities than those who received active management. Similar characteristics and outcome have been reported in other studies for those on active comfort care.[236, 243] Hence, patients who are elderly or with poor-grade aSAH are more likely to receive palliative treatment rather than early aneurysm treatment or other active treatment that may contribute to earlier death beyond the neurological insult.[243] It is difficult to disentangle the interrelationships between age and the severity of stroke with clinical decision making in a study of this kind. Arguably, management of blood pressure, nimodipine and, probably aneurysm treatment, could be given to all patients irrespective of other clinical factors. We should seek to build the evidence base for novel treatments for aSAH to improve outcomes. We should ensure that new treatments are included in clinical guidelines and that these are implemented into practice.

5.6.1 Limitations and strengths

There were some limitations of our study. Common to retrospective studies, there were missing data (≤15%) for some variables, providing a potential source of bias. Treatment of hydrocephalus is another potential process of care, but we did not have adequate information to accurately capture indication and timing. We only extracted the first reading of blood pressure from medical records in the ED because records were mostly scanned written notes rather than fully digital making accurate extraction of multiple measures difficult. Therefore, the true prevalence of hypertension may be different to that reported here. Because we did not extract details of the route of administration for nimodipine and antihypertensives we could not ascertain whether this differed by sex. Also, there were no data available for long-term functional outcomes and quality of life measures but were able to determine outcomes based on discharge destination after acute hospital admission, admittedly a poor proxy for functional status. There were several strengths of the current study. This is the first large study specifically designed to explore the association between the management of aSAH and 1-year survival after aSAH. This was a multicentre study with a large cohort of confirmed cases of aSAH. Many variables had complete, or almost complete data, for example only 1% of missing data on cause of death.

5.6.2 Conclusion

In conclusion, receipt of processes of care improved survival. However, approximately 40% of the patients with aSAH did not receive all evidence-based processes of care. There is a lack of agreement between the two guidelines regarding SBP for the receipt of antihypertensive, which needs to be addressed and updated in the guidelines. Following the guidelines may be critical to improving outcome, as processes of care were associated with reduced mortality at 1 year. We should continue to look at the new avenues for evidence-based care for aSAH patients, but also measure adherence and test interventions to address gaps in the receipt of care.

Chapter 6: Sex differences in short and long-term mortality and functional outcome after subarachnoid haemorrhage (SAH) in INternational STRoke oUtComes sTudy (INSTRUCT)-A pooled analysis of the individual participant data

6.1   Preface

The contents of this paper were circulated to the co-authors at the time of thesis submission**.**

We included other causes of SAH in the study as we could not specifically examine aSAH due to missing information on the cause of SAH in the included data sets.

Rehman S, Phan HT, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Breslin M, Callisaya ML, Vemmos K, Parmar P, Krishnamurthi R, Barker-Collo S, Feigin V, Chausson N, Olindo S, Cabral NL, Carolei A, Marini C, Sacco S, Correia M, Appelros P, Kõrv J, Vibo R, Minelli C, Sposato L, Pandian JD, Kaur P, Azarpazhooh MR, Morovatdar N, Gall S.

6.2   Abstract

Background: There have been few studies that have examined sex differences in outcomes after subarachnoid haemorrhage (SAH), particularly in the longer term. This may be due to the low incidence and relatively high case-fatality of SAH compared to ischaemic stroke. Pooling individual participant data (IPD) from people with SAH from high-quality stroke incidence studies may address this gap. We aimed to examine the short and long-term outcomes of SAH using an IPD meta-analysis.

Methods: This study is an extension of INternational STRoke oUtComes sTudy (INSTRUCT) pooling individual participant data from 13 high-quality population-based incidence studies (10 previous and 3 new studies). The primary outcomes were mortality and functional outcome (modified Rankin Scale; mRS: good outcome ≤2, poor outcome 3-5). Harmonised study factors included age, sex, behavioural factors (current smoking, alcohol intake), comorbidities (history of hypertension, ischaemic heart disease, atrial fibrillation), stroke severity (e.g. National Institutes of Health Stroke Scale [NIHSS score]) and year of SAH. In the pooled dataset, we estimated predictors of mortality, including sex, using Poisson regression, to estimate incidence rate ratio (IRR) at 1 month (11 studies), 1 year (12 studies) and 5 years (8 studies). Generalized estimating equation using the log-binomial family were used to calculate risk ratios (RRs) for predictors, including sex, of poor functional outcome at 1 month (6 studies) and 1 year (8 studies).

Results: There were n=657 people with SAH. Mortality was 33% at 1 month, 43% at 1 year, and 47% at 5 years. Poor functional outcome was 27% at 1 month and 15% at 1 year. In univariable and multivariable analysis, sex was not associated with mortality or poorer functional outcome at any time point. In multivariable analysis, mortality was predicted by age (RR 1.02 95% CI 1.01-1.03) and severity (RR 2.71 95% CI 1.98-3.72) at 1 month; age (RR 1.04 95% CI 1.03-1.05), smoking (RR 1.74 95% CI 1.11-2.72) and severity (RR 3.02 95% CI 2.03-4.48) at 1 year and; age (RR 1.04 95% CI 1.03-1.06), severity (RR 2.75 95% CI 1.56-4831), and smoking (RR 3.16 95% CI 1.58-6.31) at 5 years. Poor functional outcome was predicted by age (RR 1.03 95% CI 1.01-1.05) at 1 month and severity (RR 6.99 95% CI 2.94-16.60) at 1 year.

Conclusion: Sex did not predict mortality or poor functional outcomes after SAH. Risk factors like smoking, older age and severity of the SAH were associated with worse outcomes. Better management of older patients and those with severe strokes could improve outcomes after SAH.

6.3   Introduction

A large body of evidence exists regarding long-term outcomes of ischaemic stroke[197, 244, 245] However, few authors have examined this for subarachnoid hemorrhage (SAH). Higher mortality rates and the low incidence of SAH[246] compared to ischaemic stroke are possible explanations. Pooling individual participant data (IPD) from different studies could be a way to examine longer-term outcomes of SAH. The best source of incident cases of SAH is 'ideal' stroke incidence population-based studies.[247, 248] Salient characteristics of an ideal stroke incidence population-based study include standard definitions for stroke diagnosis (e.g. World Health Organisation definitions), first-ever cases of stroke, community-based case-ascertainment using multiple overlapping sources, prospective study design, a large and well-defined stable population, ≤ 5 years of data averaged together, ages up to ≥ 85 years. and men and women presented separately. In these studies, the likelihood of missing cases is less compared to hospital-based case-series. This is because of the community-based case ascertainment with multiple overlapping sources including death registries, which is particularly important for aSAH where sudden death without hospitalisation is not uncommon.[217] We established an IPD collaboration, the INternational STRoke oUtComes sTudy (INSTRUCT), between investigators for 13 ideal stroke incidence studies to examine sex differences in stroke. INSTRUCT provides a potential platform for examining longer-term outcomes after SAH.

Whether there are sex differences in outcomes after SAH is unclear. Only a few studies have examined sex differences in long-term outcome in SAH, such as mortality at >1 year after onset, with most reporting no difference.[74,75, 83, 84] However, none of these were designed to examine sex differences. The lack of sex differences in outcome after SAH contrasts with studies on mixed stroke cohorts that include SAH. In a previous INSTRUCT analysis, we showed that women have higher mortality[197] and greater disability than men but that this was due to sex differences in age, stroke severity, pre-stroke dependency and some risk factors[249]. However, our previous INSTRUCT study had too few SAH cases for the analysis method used and some relevant covariates were not extracted from individual studies compared to the updated data used from the studies. Therefore, a new analysis focusing on SAH could help us in elucidating sex differences in long-term outcomes.

More broadly, there are relatively few studies of the distribution and predictors of outcome of SAH, particularly in the longer term. Existing studies of long-term outcomes after SAH have

some limitations. These were mostly single-centred,[79, 84, 130] hospital-based studies,[74, 79, 130] with small sample sizes,[79, 207] examined a specific group of patients for example with less severe stroke,[75] and did not explore the association of patient-level factors[74, 83] with the outcome. This means there are gaps in our understanding of the natural history of SAH, with such data important for informing patients of their likely prognosis but also for identifying ways to improve outcomes.

In this study, we examined sex differences in short and long-term outcomes after SAH, including mortality and functional outcomes at 30 days, 1 year and 5 years.

6.4   Methods

The methods for INSTRUCT are described elsewhere[197] and registered in PROSPERO (CRD42016036723). This study is an extension of INSTRUCT including 3 new cohorts with 10 [126, 250-258] existing cohorts for a total of 13 ideal incidence stroke studies included.[126, 250-261] We performed a systematic search for new studies published between 2015-2018 (**Appendix B**) with investigators for 9 new studies contacted with 3 [262-264] agreeing to participate. We requested deidentified IPD on mortality ($\leqslant$5 years after stroke), functional outcome, quality of life (QoL) and participant characteristics. In these ideal studies, SAH diagnosis was based on a typical clinical history (headache, nausea, vomiting, decreased alertness, with or without focal neurological deficit) along with CT or lumbar puncture evidence of subarachnoid blood or angiographic demonstration of a source of bleeding[247]. Although aneurysmal rupture (85%) is the most common cause of SAH,[265] it occurs due to several other reasons like arteriovenous malformation. In this study, we examined outcomes for all causes of SAH due to the lack of more specific information on causes. INSTRUCT was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0014861). The participating studies had written informed consent and approval from their respective local ethics committees.

6.4.1   Outcome measurement

Mortality and functional outcome at 30 days, 1 year and 5 years were the outcome measures. For mortality, the sources of data in the studies were death certificates[250, 251, 253-258, 262-264], hospital records[251, 253, 258, 261-264], death registries[126, 253, 256, 257], patient follow-up[250, 254], and autopsy records[261]. Functional outcomes were assessed by the modified Rankin scale (mRS) [266, 267]. Poor outcome was defined as mRS >2 (score 0-5) [249]. For functional outcome, participants were followed up with face-to-face interviews[126, 251, 253, 254, 256, 258, 261, 268], telephone

interviews[250, 257, 262, 263] or mail[250, 257] conducted at 30 days, at 1 and 5 years after stroke. Of note, no study had Quality of Life (QoL) available for the participants with SAH.

6.4.2 Study factors

We harmonised information on study factors across studies (**Table 6-1**, **Table 6-2** and **Table 6-3**): sociodemographic factors included sex, age, marital status, race, education, and socioeconomic status; health behaviours included smoking (non-smoker, current smoker, past smoker) and alcohol use (never, daily or occasional current drinker, ex-heavy drinker); pre-stroke comorbidities comprised hypertension, ischaemic heart disease (IHD), peripheral vascular disease (PVD), transient ischaemic attack (TIA) and atrial fibrillation (AF); medications before stroke included antihypertensives, antiplatelets, and anticoagulants and year of stroke. Stroke severity was measured on different scales across the studies including the National Institutes of Health Stroke Scale score (4 studies)[250, 253, 256, 264]; Glasgow Coma Scale score (4 studies)[251, 256, 257, 261]; 6S score Stroke Severity Score based on Six Signs and Symptoms (1 study)[262], Barthel index at onset (1 study),[258] or loss of consciousness (7 studies)[126, 251, 254, 255, 261-263] and hemiplegia or motor deficit (6 studies).[126, 251, 254, 255, 261, 263] Stroke severity was categorized into two categories (less severe/more severe) using cut-off levels for different scales: National Institutes of Health Stroke Scale [NIHSS] ($\leq$7)[269]; Glasgow coma scale (GCS) [8>][270, 271]; Barthel index (BI) at onset [>20][269] or using median value (Stroke severity score SS6) or absence or presence of a loss of consciousness. Year of the SAH was categorised for analysis of each outcome at different time points. Based on available studies and number of participants, the year of SAH for mortality outcomes was categorised into five levels and for functional outcome into four levels. Year of SAH was considered as a covariate due to known trends in outcomes due to improvement in the management of SAH over time.

Table 6-1 Baseline characteristics of 13 Population-Based Stroke Incidence Studies

Study	Years of study	Region	Baseline (N)	Women %	1-month Mortality	1-year Mortality	5-year Mortality	1-month Functional outcome	1-year Functional outcome	5-year Functional outcome
Joinville, Brazil[a]	2011-2013	South America	142	55	✓	✓	✓	✓[†]	✓[§]	✓[¶]
Melbourne, Australia	1996-1999	Australasia	68	76	✓	✓	✓			
Arcadia, Greece	1993-1995	Europe	13	61		✓			✓	
Orebro, Sweden	2017	Europe	21	52	✓	✓		✓	✓	
Martinique, French West Indies	1998-1999	Caribbean	20	50	✓	✓	✓	✓	✓	✓
Porto, Portugal	1998-2000	Europe	23	78	✓	✓	✓	✓	✓	✓[¶]
Auckland, New Zealand	2002-2003	Australasia	87	53	✓	✓	✓			✓[¶¶¶]
L'Aquila, Italia	1994-1998	Europe	118	53	✓	✓	✓		✓	
Matão, Brazil	2003-2004	South America	1	0		✓				
Tartu, Estonia	2002-2003	Europe	18	72	✓	✓	✓			
Tandil, Argentina	2013-2015	South America	17	59	✓	✓		✓	✓[§§]	
Ludhiana, India	2010-2013	Asia	115	34	✓*			✓[††]		
Mashhad, Iran	2006-2007	Asia	14	43	✓	✓	✓		✓	✓
Total cases			657		632/643	542	409	222/241	210/217	73/105

Follow up data missing for: *1-month mortality for 11 cases,[†]1-month functional outcome for 8 cases; [††]1-month functional outcome for 11 cases;[§]1-year functional outcome for 1 case; [§§]1-year functional outcome for 6 cases;;[¶]5-year functional outcome for 6 cases; [¶¶]5-year functional outcome for 2 cases; [¶¶¶]5-year functional outcome for 24 cases
[a]Follow-up data to 5 years were available only among cases with year of stroke 2009 to 2011 for Joinville

Table 6-2 Characteristics of included cohort studies from Joinville, Melbourne, Arcadia, Orebro, Martinique and Porto by sex

| Characteristic | Joinville (N=142) | | Melbourne (N=68) | | Arcadia (N=13) | | Orebro (N=21) | | Martinique (N=20) | | Porto (N=23) | |
	Men (n=64) N(%)*	Women (n=78) N(%)*	Men (n=16) N(%)*	Women (n=52) N(%)*	Men (n=5) N(%)*	Women (n=8) N(%)*	Men (n=10) N(%)*	Women (n=11) N(%)*	Men (n=10) N(%)*	Women (n=10) N(%)*	Men (n=5) N(%)*	Women (n=18) N(%)*
Age, Mean (SD)	54 (14.31)	52.34 (12.54)	58.46 (15.63)	59.22 (17.40)	71.40 (12.11)	68.87 (9.44)	59.70 (19.71)	64.63 (14.98)	44.50 (20.00)	60.30 (14.05)	63.40 (19.80)	58.61 (18.90)
Race												
Caucasian	-	-	15(94)	46(88)	-	-	8(80)	11(100)	0	0	-	-
Non-Caucasian			1(6)	2(3)			2(20)	0	10(100)	10(100)		
Missing			0	4(8)			0	0	0	0		
Marital status												
No (single/widowed/divorced)	-	-	-	-	-	-	1(10)	5(45)	-	-	-	-
Yes							9(90)	6(55)				
Missing							0	0				
Education												
≤ Grade12	60(94)	66(85)	2(13)	3(6)	-	-	-	-	-	-	3(60)	12(67)
> Grade12	3(5)	11(14)	14(87)	49(94)							1(20)	1(5)
Missing	1(1)	1(1)	0	0							1(20)	5(28)
Hypertension history												
No	34(53)	35(45)	10(63)	34(65)	1(20)	1(13)	6(60)	6(54)	8(80)	3(30)	1(20)	13(72)
Yes	30(46)	43(55)	5(31)	15(29)	4(80)	7(87)	4(40)	4(36)	2(20)	7(70)	4(80)	5(28)
Missing	0	0	1(6)	3(6)	0	0	0	1(9)	0	0	0	0
History of diabetes												
No	-	-	13(81)	47(90)	1(20)	6(75)	-	-	10(100)	9(90)	-	-
Yes			2(12)	2(4)	4(80)	2(25)			0	1(10)		
Missing			1(6)	3(6)	0	0			0	0		
Smoking												
Never	17(26)	38(49)	1(6)	23(44)	3(60)	7(87)	8(80)	7(64)	-	-	3(60)	16(89)
Former	16(25)	8(10)	6(38)	3(6)	0	0	0	0			0	0
Current	31(48)	32(41)	4(25)	10(19)	2(40)	1(13)	2(20)	3(27)			2(40)	2(11)
Missing	0	0	5(31)	16(31)	0	0	0	1(9)			0	0
Alcohol												
Never	22(34)	55(71)	0	14(27)	3(60)	8(100)	0	0	6(60)	8(80)	2(40)	8(44)
Current drinker	42(66)	23(29)	10(63)	19(36)	2(40)	0	8(80)	3(27)	4(40)	2(20)	3(60)	6(33)

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Characteristic	Joinville (N=142) Men (n=64) N(%)*	Women (n=78) N(%)*	Melbourne (N=68) Men (n=16) N(%)*	Women (n=52) N(%)*	Arcadia (N=13) Men (n=5) N(%)*	Women (n=8) N(%)*	Orebro (N=21) Men (n=10) N(%)*	Women (n=11) N(%)*	Martinique (N=20) Men (n=10) N(%)*	Women (n=10) N(%)*	Porto (N=23) Men (n=5) N(%)*	Women (n=18) N(%)*
(Occasional/ daily)												
Ex-heavy drinker	0	0	1(6)	0	0	0	0	0	0	0	0	0
Missing	0	0	5(31)	19(36)	0	0	2(20)	8(72)	0	0	0	4(22)
Transient Ischaemic Attack												
No	64(100)	78(100)	16(100)	51(98)	5(100)	8(100)	10(100)	11(100)	10(100)	10(100)	5(100)	18(100)
Yes	0	0	0	1(2)	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0	0	0
Atrial fibrillation												
No	63(98)	78(100)	14(87)	47(90)	4(80)	8(100)	10(100)	9(81)	10(100)	10(100)	5(100)	18(100)
Yes	1(2)	0	0	1(2)	1(20)	0	0	2(19)	0	0	0	0
Missing	0	0	2(13)	4(8)	0	0	0	0	0	0	0	0
Ischaemic heart disease												
No	62(97)	78(100)	15(94)	50(96)	4(80)	7(87)	8(80)	3(27)	10(100)	10(100)	4(80)	18(100)
Yes	2(3)	0	1(6)	0	1(20)	1(13)	0	0	0	0	1(20)	0
Missing	0	0	0	2(4)	0	0	2(20)	8(73)	0	0	0	0
Peripheral vascular disease												
No	-	-	14(87)	49(94)	5(100)	8(100)	8(80)	3(27)	10(100)	10(100)	5(100)	17(94)
Yes			2(13)	1(2)	0	0	0	0	0	0	0	0
Missing			0	2(4)	0	0	2(20)	8(73)	0	0	0	1(6)
Stroke severity			0	0	0	0	0	0	0	0	0	0
NIHSS Mean (SD)	14.21 (11.91)	14.01 (11.37)	5.42 (11.42)	9.40 (12.21)			1.28 (1.49)	26.33 (7.76)				
NIHSS												
Less severe	30(47)	32(41)	6(37)	13 (25)			7(70)	0				
More severe	34(53)	46(59)	1(1)	9(17)			0	3(27)				
Missing			9(56)	30(57)			3(30)	8(72)				
GCS Mean (SD)					8.00 (5.56)	7.12 (3.87)						
GCS												
Less severe					2(40)	3(37)						
More severe					3(60)	5(62)						

Characteristic	Joinville (N=142) Men (n=64) N(%)*	Women (n=78) N(%)*	Melbourne (N=68) Men (n=16) N(%)*	Women (n=52) N(%)*	Arcadia (N=13) Men (n=5) N(%)*	Women (n=8) N(%)*	Orebro (N=21) Men (n=10) N(%)*	Women (n=11) N(%)*	Martinique (N=20) Men (n=10) N(%)*	Women (n=10) N(%)*	Porto (N=23) Men (n=5) N(%)*	Women (n=18) N(%)*
Missing					0	0						
Loss of consciousness												
No	-	-	6(37)	19(36)	4(80)	7(87)	-	-	-	-	5(100)	14(78)
Yes			7(44)	24(46)	1(20)	1(13)					0	4(22)
Missing			3(19)	9(17)	0	0					0	0
Loss of consciousness												
Less severe												
More severe												
Missing												
Barthel index at onset												
<20	-	-	-		-	-	-	-	3(30)	2(20)	-	-
≥20									1(10)	2(20)		
Missing									6(60)	6(60)		
Paralysis/motor deficit												
No	-	-	10(62)	27(52)	1(20)	3(37)	-	-	-	-	5(100)	18(100)
Yes			3(19)	16(31)	4(80)	5(63)					0	0
Missing			3(19)	9(17)	0	0					0	0

*Otherwise indicated

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Table 6-3 Characteristics of included cohort studies from Auckland, L'Aquila, Matao, Tartu, Tandil, Ludhiana and Mashhad by sex

Characteristic	Auckland (N=87) Men (n=41) N(%)*	Women (n=46) N(%)*	L'Aquila (N=118) Men (n=55) N(%)*	Women (n=63) N(%)*	Matao (N=1) Men (n=1) N(%)*	Women (n=0) N(%)*	Tartu (N=18) Men (n=5) N(%)*	Women (n=13) N(%)*	Tandil (N=17) Men (n=7) N(%)*	Women (n=10) N(%)*	Ludhiana (N=115) Men (n=76) N(%)*	Women (n=39) N(%)*	Mashhad (N=14) Men (n=8) N(%)*	Women (n=6) N(%)*
Age Mean (SD)	57.56 (14.73)	60.06 (16.04)	56.18 (16.85)	64.80 (13.96)	83	-	59.80 (12.75)	61.30 (12.65)	60.57 (20.63)	60.10 (21.90)	47.39 (16.19)	48.23 (16.05)	50.62 (17.14)	51.66 (10.89)
Race														
Caucasian	8(20)	9(19)	-	-	-	-	-	-	-	-	-	-	0	0
Non-Caucasian	2(5)	3(7)											8(100)	6(100)
Missing	31(75)	34(74)											0	0
Marital status														
No (single/ widowed/ divorced)	11(27)	20(43)	-	-	-	-	-	-	-	-	2(3)	3(8)	1(12)	1(17)
Yes	30(73)	23(50)	-	-	-	-	-	-	-	-	43(55)	22(56)	7(88)	5(83)
Missing	0	3(7)									32(42)	14(35)	0	0
Education														
≤ Grade12	8(20)	14(30)			1(100)	0	-	-	-	-	40(53)	23(59)	6(75)	5(83)
> Grade12	17(41)	13(28)									3(4)	0	2(25)	1(17)
Missing	16(39)	19(41)									33(43)	16(41)	0	0
Hypertension history														
No	23(56)	25(54)	23(42)	25(40)	1(100)	-	3(60)	6(46)	3(43)	4(40)	2(3)	2(5)	7(88)	2(33)
Yes	13(32)	18(39)	31(56)	38(60)			2(40)	7(54)	4(57)	6(60)	42(55)	23(59)	1(12)	4(67)
Missing	5(12)	3(6)	1(2)								32(42)	14(36)		
History of diabetes														
No	-	-	-	-	-	-	-	-	-	-	33(43)	15(38)	8(100)	6(100)
Yes											11(15)	10(26)	0	0
Missing											32(42)	14(36)	0	0
Smoking														
Never	10(24)	16(35)	28(51)	43(68)	1(100)	0	-	-	7(100)	9(90)	26(34)	24(61)	5(62)	4(67)
Former	17(41)	8(17)	0	0	0	0			0	0	12(16)	0	0	0
Current	7(17)	15(33)	17(31)	5(8)	0	0			0	1(10)	5(7)	1(3)	3(37)	2(33)
Missing	7(17)	7(15)	10(18)	15(24)	0	0			0	0	33(43)	14(36)	0	0
Alcohol														

Characteristic	Auckland (N=87) Men (n=41) N(%)*	Women (n=46) N(%)*	L'Aquila (N=118) Men (n=55) N(%)*	Women (n=63) N(%)*	Matao (N=1) Men (n=1) N(%)*	Women (n=0) N(%)*	Tartu (N=18) Men (n=5) N(%)*	Women (n=13) N(%)*	Tandil (N=17) Men (n=7) N(%)*	Women (n=10) N(%)*	Ludhiana (N=115) Men (n=76) N(%)*	Women (n=39) N(%)*	Mashhad (N=14) Men (n=8) N(%)*	Women (n=6) N(%)*
Never	6(15)	15(33)	-	-	1(100)	0	-	-	6(86)	10(100)	7(9)	24(61)	8(100)	6(100)
Current drinker (Occasional/ daily)	20(49)	15(33)			0	0			1(14)	0	12(16)	0	0	0
Ex-heavy drinker	4(10)	5(11)			0	0			0	0	20(30)	1(3)	0	0
Missing	11(26)	11(24)			0	0			0	0	24(45)	14(36)	0	0
Transient Ischaemic Attack														
No	-	-	49(89)	60(95)	1(100)	0	-	-	6(86)	10(100)	35(46)	20(51)	8(100)	6(100)
Yes			0	0	0	0			1(14)	0	9(12)	5(13)	0	0
Missing			6(11)	3(5)	0	0			0	0	32(42)	14(36)	0	0
Atrial fibrillation														
No	40(98)	41(89)	50(91)	55(87)	1(100)	0	-	-	6(86)	10(100)	39(51)	22(56)	7(87)	6(100)
Yes	0	3(7)	2(4)	5(8)	0	0			1(14)	0	5(6)	3(8)	1(13)	0
Missing	1(20	2(4)	3(5)	3(5)	0	0			0	0	32(42)	14(36)	0	0
Ischaemic heart disease														
No	37(90)	42(91)	47(85)	53(84)	1(100)	-	-	-	-	-	37(48)	24(61)	-	-
Yes	3(7)	3(7)	3(5)	6(10)	0						7(9)	1(2)		
Missing	1(2)	1(2)	5(9)	4(6)	0						32(42)	14(36)		
Peripheral vascular disease														
No	-	-	49(89)	55(87)	1(100)	0	-	-	-	-	-	-	-	-
Yes			1(2)	3(5)	0	0								
Missing			5(9)	5(8)	0	0								
Stroke severity														
NIHSS mean (SD)	-	-	-	-	22	-	-	-	-	-	-	-	6.28 (13.25)	4.5 (10.54)
NIHSS														
Less													6(75)	5(83)
Severe					1 (100)								0	1(16)
Missing													2(25)	0
GCS mean (SD)	5.45 (5.03)	6.14 (4.63)	-	-	9	-	13.4 (2.07)	11.18 (4.99)	-	-	-	-	-	-

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Characteristic	Auckland (N=87) Men (n=41) N(%)*	Women (n=46) N(%)*	L'Aquila (N=118) Men (n=55) N(%)*	Women (n=63) N(%)*	Matao (N=1) Men (n=1) N(%)*	Women (n=0) N(%)*	Tartu (N=18) Men (n=5) N(%)*	Women (n=13) N(%)*	Tandil (N=17) Men (n=7) N(%)*	Women (n=10) N(%)*	Ludhiana (N=115) Men (n=76) N(%)*	Women (n=39) N(%)*	Mashhad (N=14) Men (n=8) N(%)*	Women (n=6) N(%)*
GCS														
Less	13(31)	15 (33)					5 (100)	8 (61)						
Severe	24 (58)	26 (56)					0	3(23)						
Missing	4 (10)	5 (11)					0	2(15)						
Loss of consciousness														
No	11(27)	8(17)	20(36)	28(44)	-	0	-	-	2(29)	10(100)	23(30)	13(33)	-	-
Yes	28(68)	34(74)	33(60)	35(56)					5(71)	0	20(26)	12(31)		
Missing	2(5)	4(9)	2(4)	0					0	0	33(43)	14(36)		
6S score Mean (SD)	-	-	-	-	-	-	-	-	3.71 (2.13)	4.88 (1.45)	-	-	-	-
6S score														
Less severe									5(71)	6(60)				
More severe									2(28)	3(30)				
Missing										1(10)				
Paralysis/motor deficit														
No	16(39)	19(41)	40(73)	51(81)	-	-	-	-	-	-	13(17)	8(20)	-	-
Yes	21(51)	22(48)	11(20)	9(14)							30(39)	17(44)		
Missing	4(10)	5(11)	4(7)	3(5)							33(43)	14(36)		

*Otherwise indicated

**6S score; Stroke Severity Score based on Six Signs and Symptoms

6.4.3 Statistical analysis

We created a pooled dataset with people with SAH from 13 datasets. Poisson regression was used for calculating the incidence rate ratio of mortality by study factors with the cohort as a cluster variable, at 30 days (11 studies), 1 year (12 studies) and 5 years (8 studies) after stroke with the logarithm of the number of person-years at risk of dying within that period entered as an offset. For functional outcome, we used generalized equation estimates using binomial family and population cohorts as clusters to calculate risk ratio of poor outcome (modified Rankin Scale>2) by study factors at 30 days (6 studies) and 1 year (8 studies).

To examine the role of sex in the outcome, we used a purposeful model building. We included a variable in the multivariable model when (1) the covariate was associated with sex (p-value $\leqslant 0.25$), (2) the covariate was associated with the outcome (p-value $\leqslant 0.25$), and (3) the covariate changed the effect of sex on the outcome by $\geqslant 10\%$.[206]

We performed a sensitivity analysis to examine the effect of different severity scales on the outcomes. Statistical interaction was tested between sex and covariates using product terms. We forced the severity of SAH and time-periods of SAH into the multivariable model.[197]

Multiple imputations by chained equations (m=30 imputations) using variables with complete data (sex, age, mortality, and year of stroke) were used to impute person-years in Poisson model when date of death was not provided. The imputations were also performed for covariates and outcomes when missing data was present for more than 20% of cases.[197] The effect of missing data on results was examined by comparing complete case and imputed analyses for univariable and multivariable models for each outcome at each time points.

Analyses were conducted in Stata 16 (StataCorp LLC, Texas, USA) and two-tailed p-value <0.05 was considered statistically significant.

6.5 Results

In total, we included 13 studies with 657 participants across 3 new and 10 existing studies in INSTRUCT (**Figure 6-1**). The characteristics of participants with SAH are provided in **Table 6-4 .**
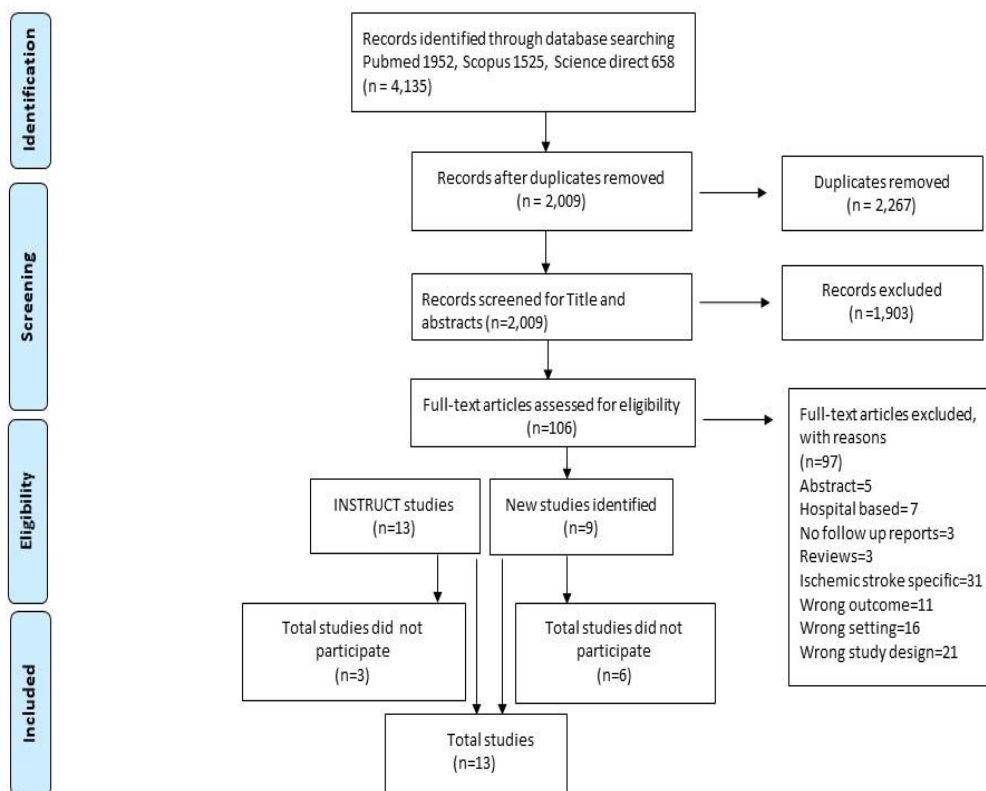
Figure 6-1 Flow chart showing the selection of the studies

Women comprised a greater proportion (46% men vs 54% women) of the cohort. Mean age for the cohort was 56 years. In this cohort 22% were married and 18% had education beyond grade 12 but the missing data was more than 40% for these covariates. In this pooled cohort 48% were hypertensive, 22% were current smokers and 10% were past smokers, current alcohol intake was present in 25% of the patients. Other covariates like diabetes mellitus, TIA, AF and PVD were present in <5%. Around 44% suffered from severe stroke compared to 41% who had a less severe one.

Compared to men (mean age 54 years), women were older (57 years, p 0.002), less likely to be married (29% men vs 16% women, p<0.001) and had more education after year 12 (13% men vs 21% women, p=0.009), noting missing data for these factors. More men were past (17% men vs 5%women) and current smokers (24% men vs 20% women, p <0.001) compared to women. Current alcohol drinking was also more common in men compared to women (34% men vs 19% women, p<0.001). After harmonising severity scores, 'severe' stroke was not different by sex (41% men vs 46% women, p=0.47). Other covariates like hypertension history, diabetes mellitus, TIA, AF and PVD were not different by sex. The details for each study are provided in **Table 6-1**, **Table 6-2** and **Table 6-3** and in **Figure 6-2** and **Figure 6-3**. The distribution of sex according to year of stroke is shown in **Table 6-5**.
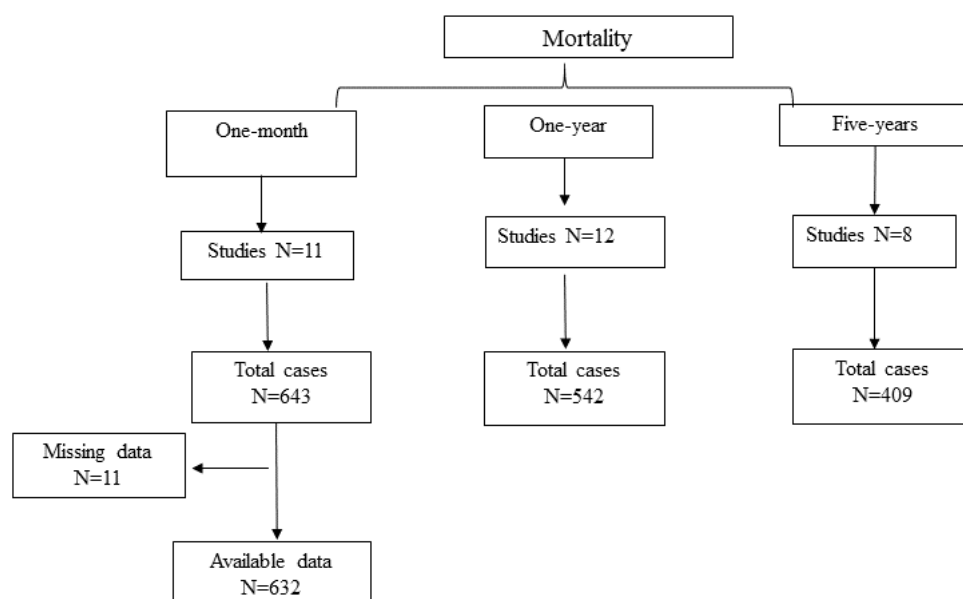
Figure 6-2 Flow chart of studies with available and missing data on mortality
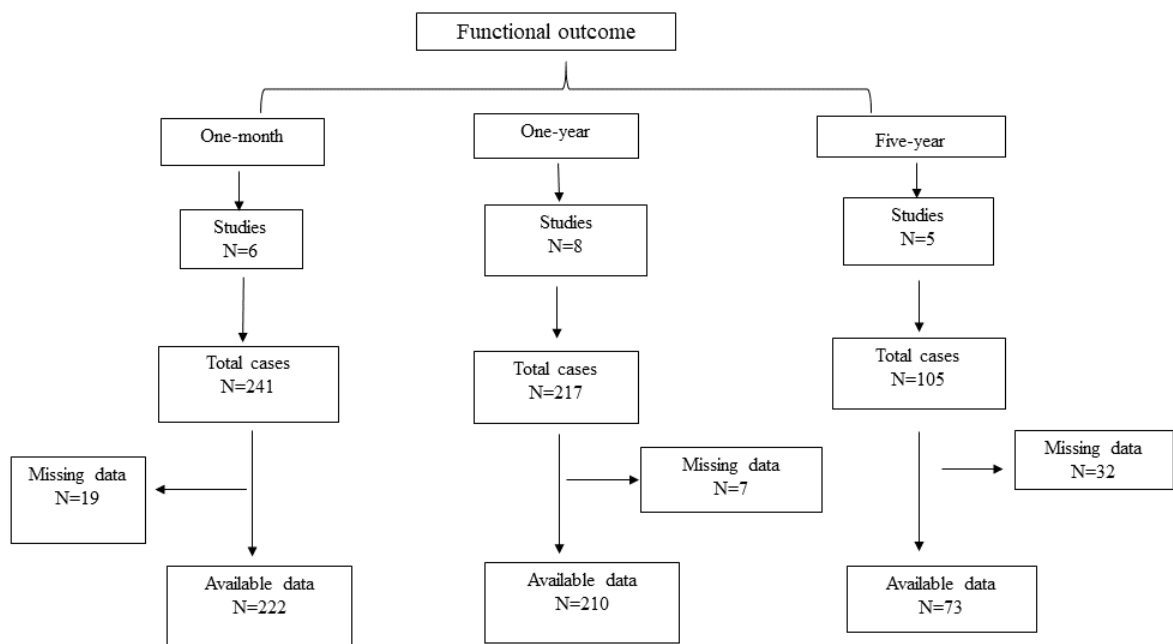
Figure 6-3 Flow chart of studies with available and missing data on functional outcome

Table 6-4 Characteristics of men and women with first-ever SAH from 13 Population-based Stroke Incidence Studies (N=657)

Variable	Total N=657		Men N=303 (46%)		Women N=354 (54%)		P-value
	N	%	N	%	N	%	
Age, mean (SD)	56	16	54	16	57	15	0.002
Marital status							<0.001
Single/widowed/divorced	44	7	15	5	29	8	
Married	145	22	89	29	56	16	
Missing	468	71	199	66	269	76	
Education							0.009
No	243	37	120	40	123	35	
Yes>12year	115	18	40	13	75	21	
Missing	299	45	143	47	156	44	
Hypertension history							0.87
No	278	42	122	40	156	44	
Yes	319	48	142	47	177	50	
Missing	60	9	39	13	21	6	
History of diabetes							0.34
No	148	73	65	21	83	23	
Yes	32	2	17	6	15	4	
Missing	477	72	221	73	256	72	
Smoking							<0.001
Never	296	45	109	36	187	53	
Former	70	10	51	17	19	5	
Current	145	22	73	24	72	20	
Missing	146	22	70	23	76	21	
Alcohol							<0.001
Never	209	32	61	20	148	41	
Current drinker (occasional/daily)	170	25	102	34	68	19	
Ex-heavy drinker	34	5	28	9	6	2	
Missing	244	37	112	37	132	37	
Transient Ischaemic Attack							0.13
No	481	73	209	69	272	77	
Yes	16	2	10	3	6	2	
Missing	160	24	84	28	76	21	
Atrial fibrillation							0.74
No	553	84	249	82	304	86	
Yes	24	4	10	3	14	4	
Missing	80	12	44	14	36	10	
Ischaemic heart disease							0.06
No	510	78	225	74	285	80	
Yes	29	4	18	6	11	3	
Missing	118	18	60	20	58	16	
Peripheral vascular disease							0.85
No	234	35	92	30	142	40	
Yes	7	1	3	1	4	1	
Missing	416	63	208	69	208	59	

Variable	Total N=657		Men N=303 (46%)		Women N=354 (54%)		P-value
	N	%	N	%	N	%	
Stroke severity							0.47
Less severe	270	41	125	41	145	41	
More severe	289	44	125	41	164	46	
Missing	98	15	53	17	45	13	

Table 6-5 Year of SAH event

Year of SAH	Total		Men		Women	
	N	**%**	**N**	**%**	**N**	**%**
1993-1999	234	36	90	30	144	41
2000-2009	135	20	58	19	77	22
2010-2017	285	43	154	51	131	37
Missing	3	0.4	1	0.3	2	0.5

*year of stroke missing for 3 patients at 1 month

6.5.1 Mortality

At 1 month, 33% (n/N=215/643) of people with SAH died. Mortality rate was similar in both sexes at 1 month (36% women vs 30% men, p=0.09) after SAH (**Figure 6-4, Panel A**). There were missing data for study factors reducing the sample size for the multivariable analysis. Using the imputed dataset, in univariable and multivariable analysis (**Table 6-6**), the risk ratio of mortality in women was somewhat elevated but not statistically different to men at 1 month (MRR$_{unadjusted}$ 1.28 95% CI 0.97-1.70; MRR$_{adjusted}$ 1.21 95% CI 0.92-1.61). Greater age and more severe stroke were independently associated with higher mortality at 1 month after stroke.

At 1 year, 43% (n/N=230/542) of participants with SAH were deceased. The mortality rate was similar in both sexes at 1 year following SAH (44% women vs 41% men, p=0.55). Using the imputed dataset, there was no sex difference in 1-year mortality rate ratio MRR$_{unadjusted}$ 1.09 95% CI 0.83-1.44; MRR$_{adjusted}$ 1.05 95% CI 0.73-1.49) in the univariable and multivariable analysis but current smoking and more severe stroke independently predicted this outcome (**Table 6-6**).

At 5 years, 47% (n/N=193/409) participants had died**.** There was no difference by sex in mortality rate at 5 years following SAH (47% in men and women, p=0.95). Using the imputed dataset, in univariable and multivariable analysis, the sex differences were not significant for mortality at 5 years (MRR$_{unadjusted}$ 1.06 95% CI 0.79-1.42; MRR$_{adjusted}$ 1.34 95% CI 0.74-2.35). Greater age, current smoking, and more severe stroke were predictors of mortality at 5 years (**Table 6-6**). The results between the complete case and imputed analysis in univariable and multivariable models for mortality at multiple time points were observed to be almost identical (data not shown).
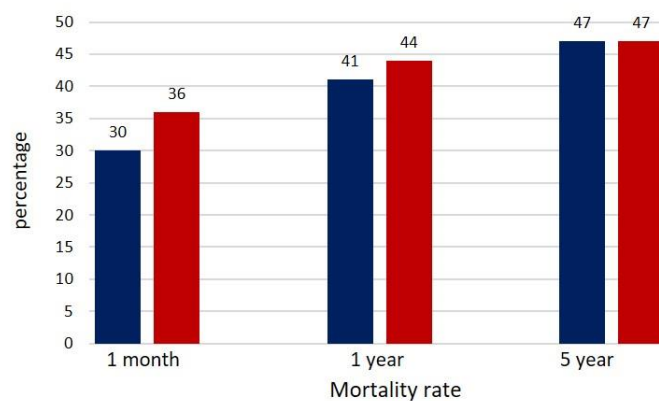
6.5.2 Functional Outcome

At 1 month, 27% (n/N=66/241) of people with SAH had a poor functional outcome. The proportion of people with poor functional outcome was similar in men and women (32% men vs 34% women, p=0.54). See **Figure 6-4**, **Panel B**. At 1 month, using the imputed dataset for univariable analysis and multivariable analysis (**Table 6-7**), the risk of poor functional outcome was not different by sex (RR$_{unadjusted}$ 1.04 95% CI 0.70-1.52; RR$_{adjusted}$ 1.19 95% CI 0.72-1.95) but older age was associated with greater risk of poor functional outcome at 1 month.

At 1 year, 15% (n/N=33/217) of patients had a poor functional outcome. The proportion of people with poor functional outcome was higher in women than men but not statistically

significantly different at 1 year (10% men vs 19% women, p=0.07). At 1 year in univariable analysis and multivariable analysis using the imputed data (**Table 6-7**), the risk of poor functional outcome was similar between the sexes ($RR_{unadjusted}$ 1.69 95% CI 0.85-3.36; $RR_{adjusted}$ 1.54 95% CI 0.73-3.25). In multivariable analysis, stroke severity was the only independent predictor of the risk of poor functional outcome. The results between the complete case and imputed analysis in univariable and multivariable models for the poor outcome at multiple time points were observed to be almost identical (data not shown).

In sensitivity analysis examining individual rather than harmonised severity scores, the different measures of severe stroke were generally associated with the poor outcomes except when the score was provided by one study and the sample size was very small (6SSS and Barthel Index at the onset, **Table 6-8** and **Table 6-9**).
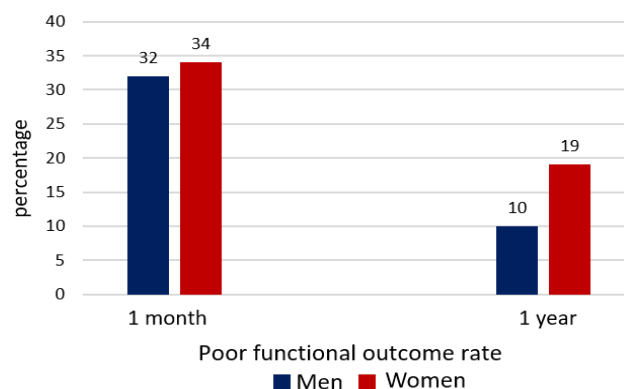
Panel A

Panel B

Figure 6-4 Mortality in men and women (Panel A) at 1 month (n/N=215/643, 11 studies); 1 year (n/N=230/542, 12 studies) and 5 year (n/N=193/409, 8 studies) and poor functional outcome in men and women (Panel B) at 1 month (n/N=66/241, 6 studies) and 1 year (n/N=33/217, 8 studies)

Table 6-6 Mortality rate ratio (MRR) after SAH in women compared to men in univariable and multivariable analysis

Variable	MRR at 1 month (N=643, 11 studies)		MRR at 1 year (N=542, 12 studies)		MRR at 5 years (N=409, 8 studies)	
	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR* (95% CI)
Female sex	1.28 (0.97-1.70)	1.21 (0.92-1.61)	1.09 (0.83-1.44)	1.05 (0.73-1.49)	1.06 (0.79-1.42)	1.34 (0.74-2.35)
Age	**1.03 (1.0-1.04)**	**1.02 (1.01-1.03)**	**1.04 (1.03-1.05)**	**1.04 (1.03-1.06)**	**1.04 (1.03-1.06)**	**1.04 (1.03-1.06)**
Hypertension history						
No	Ref		Ref		Ref	
Yes	1.24 (0.91-1.68)		**1.54 (1.17-2.04)**		**1.98 (1.46-2.68)**	
Smoking						
Never	Ref		Ref		Ref	
Former	0.74 (0.43-1.25)		0.69 (0.39-1.24)	0.68 (0.35-1.29)	0.75 (0.42-1.38)	0.94 (0.31-2.77)
Current	1.08 (0.76-1.53)		1.23 (0.89-1.71)	**1.74 (1.11-2.72)**	1.37 (0.95-1.95)	**3.16 (1.58-6.31)**
Alcohol						
Never	Ref		Ref		Ref	
Current drinker (occasional or daily)	0.96 (0.66-1.39)		0.76 (0.54-1.09)		0.97 (0.64-1.46)	
Ex-heavy drinker	0.69 (0.33-1.45)		0.59 (0.19-1.89)		0.81 (0.24-2.71)	
Transient Ischaemic Attack						
No	Ref					
Yes	0.69 (0.24-2.01)		**-**		-	
Atrial fibrillation						
No	Ref		Ref		Ref	

Variable	MRR at 1 month (N=643, 11 studies)		MRR at 1 year (N=542, 12 studies)		MRR at 5 years (N=409, 8 studies)	
	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR* (95% CI)
Yes	1.28 (0.65-2.52)		**2.08 (1.13-3.82)**		1.89 (0.92-3.82)	
Ischaemic heart disease						
No	Ref		Ref		Ref	
Yes	1.65 (0.94-2.92)		**2.04 (1.07-3.88)**		1.62 (0.87-3.00)	
Stroke severity						
Less severe	Ref		Ref		Ref	
More severe	**2.87(2.09-3.93)**	**2.71 (1.98-3.72)**	**3.79 (2.79-5.15)**	**3.02 (2.03-4.48)**	**2.57 (1.80-3.66)**	**2.75 (1.56-4.83)**

*Adjusted for time-period of stroke

For Joinville study, follow-up data to 5 years were available only among cases with year of stroke 2009 to 2011

Table 6-7 Relative risk of having poor functional outcome (mRS >2) for women compared to men among survivors after SAH in univariable and multivariable analysis

Variable	1 month (n=241, 6 studies)		1 year (n=217, 8 studies)	
	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR* (95% CI)
Female sex	1.04 (0.70-1.52)	1.19 (0.72-1.95)	1.69 (0.85-3.36)	1.54 (0.73-3.25)
Age	**1.03 (1.01-1.04)**	**1.03 (1.01-1.05)**	**1.03 (1.01-1.05)**	
Hypertension history				
No	Ref		Ref	
Yes	1.28 (0.82-2.03)		1.38 (0.74-2.60)	
Smoking				
Never	Ref		Ref	
Former	0.75 (0.37-1.51)		0.39 (0.05-2.92)	
Current	0.84 (0.49-1.43)		0.48 (0.20-1.17)	
Alcohol				
Never	Ref		Ref	
Current drinker (occasional or daily)	0.80 (0.49-1.30)		0.45 (0.16-1.21)	
Ex-heavy drinker	0.78 (0.30-2.05)		-	
Transient Ischaemic Attack				
No	Ref			
Yes	1.18 (0.49-2.83)		-	
Atrial fibrillation				
No	Ref			
Yes	0.92 (0.29-2.96)		-	
Ischaemic heart disease				
No	Ref			

Yes	0.88 (0.15-4.93)	-	
Stroke severity			
Less severe	Ref	Ref	
More severe	**1.90 (1.21-2.97)**	**6.78 (2.97-15.46)**	**6.99 (2.94-16.60)**

*Adjusted for time-period of stroke

For Joinville study, follow-up data to 5 years were available only among cases with the year of stroke 2009 to 2011

Table 6-8 Rate ratio of severity scores after SAH in univariable and multivariable analysis for mortality at multiple time points

Variable	1 month Univariable RR (95% CI)	Multivariable RR* (95% CI)	1 year Univariable RR (95% CI)	Multivariable RR** (95% CI)	5 years Univariable RR (95% CI)	Multivariable RR*** (95% CI)
Stroke severity scores						
NIHSS ⩽ 7	Ref		Ref		Ref	
NIHSS > 7	**1.11 (1.08-1.15)**	**1.11 (1.08-1.14)**	**1.16 (1.13-1.18)**	**1.17 (1.14-1.20)**	**1.13 (1.11-1.15)**	**1.16 (1.14-1.18)**
GCS > 8	Ref		Ref		Ref	
GCS ⩽ 8	**1.07 (1.01-1.13)**	1.08 (0.99-1.19)	1.00 (0.96-1.03)	1.01 (0.98-1.05)	**1.02 (1.00-1.04)**	**1.02 (1.00-1.04)**
6 SSS ⩽ 4	Ref		Ref			
6 SSS > 4	1.62 (0.96-2.72)	**1.77 (1.03-3.04)**	1.39 (0.93-2.09)	1.30 (0.90-1.90)		
No loss of consciousness	Ref		Ref		Ref	
Loss of consciousness	**2.86 (2.41-3.39)**	**3.17 (2.48-4.04)**	**5.58 (4.62-6.73)**	**4.63 (4.14-5.19)**	**4.27 (3.82-4.75)**	**3.86 (3.47-4.29)**

*Adjusted for age, sex and time-period of stroke, ** Adjusted for age, sex, smoking and time-period of stroke, *** Adjusted for age, sex, smoking, and time-period of stroke

Table 6-9 Rate ratio of severity scores after SAH in univariable and multivariable analysis for poor functional outcome (>2mRS) at multiple time points

Variable	1 month		1 year	
	Univariable RR (95% CI)	Multivariable RR* (95% CI)	Univariable RR (95% CI)	Multivariable RR** (95% CI)
Stroke severity scores				
NIHSS ≤ 7	Ref		Ref	
NIHSS > 7	**1.04 (1.01-1.08)**	**1.08 (1.03-1.13)**	**1.08 (1.04-1.12)**	**1.05 (1.04-1.14)**
No loss of consciousness			Ref	
Loss of consciousness	1.04 (0.55-1.98)	1.50 (0.51-4.34)	**7.41 (2.24-24.46)**	**7.34 (2.19-24.61)**

*Adjusted for age, sex and time-period of stroke**Adjusted for sex and time-period of stroke

6.6   Discussion

This is one of the largest studies of SAH outcomes at multiple time points from population-based datasets. Sex was not a statistically significant factor contributing to outcomes after SAH. Age, stroke severity, and current smoking were independent predictors of death at multiple time points. Poor functional outcome was more common in older people and those with more severe strokes. Our study confirms high levels of case-fatality and poor functional outcome in the longer term after SAH.

Sex was not an independent predictor of mortality at any of the multiple time points. Studies have reported inconsistent findings regarding sex differences in case fatality at less than 1 year[64, 65, 69, 71] and after 1 year of onset SAH.[75, 82, 83] Several studies have reported no significant difference in survival after SAH by sex. In one hospital-based prospective Dutch study with 1,761 participants, mortality within 1 year in women was RR 0.90 (95% CI 0.785-1.03) compared to men.[69] Similarly, the rate of mortality within 30 days was greater in men (34%) compared to women (19%) in a retrospective hospital-based study comprising of 121 patients from Martinique, but this difference was not statistically significant noting the small sample size and limited power to detect a difference in that study.[71] In other studies, differences between men and women in survival after SAH have been found. In one hospital-based study with prospectively collected data of 752 patients in the Netherlands, the long term standardised mortality ratio in women was greater (SMR 2.0 95% CI 1.6 to 2.6) compared to men (SMR 1.3 95% CI 0.9 to 1.8).[82] While authors of another hospital-based study on 1,746 participants in Finland, reported male sex as an independent predictor for the long-term relative excess risk of mortality after SAH (RER 1.6 95% CI 1.0-2.7).[83] Of note, most of these studies were not aimed at examining the role of sex in the outcome, meaning they may have reported the sex difference as part of analyses focused on a different exposure or all predictors. In these studies, the sex difference, if it exists, might be masked by other variables in a model. The existing studies were also not population-based, potentially introducing bias that may hamper the ability to see sex differences in outcome after SAH. In the current study, we were focused on identifying sex differences in outcomes and used data from population-based studies. However, we also failed to find any sex difference in survival after SAH.

Poor functional outcome was similar in both sexes, evident in 27% at 1 month and 15% at 1 year among survivors. Noting that the populations are not identical over the time-periods due to different studies included at different time points, these figures are similar to those

previously reported from individual studies.[272-274] Other hospital-based studies have shown that there is no sex difference in functional outcome at 3 months[52] and up to 1 year.[275] Thus, outcome after SAH appears to be independent of sex. Highlighting that these data do not represent one cohort followed over time, there is an apparent reduction in poor functional outcome over time. This might be due to survivor bias where those that have the worst functional levels are less likely to survive in the longer term. This, therefore, leaves a cohort of people with SAH with less functional limitations surviving longer. However, longitudinal studies with repeated assessments of outcome are needed to properly address this question.

The study factors that were identified as potential confounders of the association between sex and outcomes provide further insights into predictors of outcome after SAH. Advancing age and severity of SAH were predictors of mortality at all time points and poor functional outcome was predicted by age at 1 month and severity at 1 year. Current smoking was an additional predictor of mortality at 1 and 5 years after SAH. These predictors are consistent with other studies.[276-278]

Age is a well-known factor associated with mortality and poor functional outcome after SAH.[87, 224, 277, 279,280 281, 282] This is because increasing age is associated with comorbidities[243, 283, 284] and suffering more severe SAH[285] and that leads to an increased risk of death or poor functional recovery. Compared to the brains of younger people, the aging brain may have a more limited ability to repair structural or functional damage after SAH.[87] Some studies have reported that older people more commonly suffer complications of SAH associated with mortality like shunt-dependent hydrocephalus[110, 286] and rebleeding[287, 288] potentially explaining worse outcome in older patients. We could not examine this in the current study because the included datasets did not collect complications. It has also been observed that elderly patients less often have their aneurysm secured than younger patients after SAH. It has been speculated that this is due to concern about higher mortality rates in older compared to younger patients.[289] The rate of death after neurosurgical or endovascular treatment for SAH has reduced over time due to improvements in techniques.[290, 291] Importantly, studies have shown good outcomes for people with SAH from active management including surgery even when there was a considerable proportion of elderly patients.[289] Ensuring evidence-based management in older patients with SAH will lead to better survival and good functional outcomes.

The severity of SAH was independently associated with mortality[224, 278] and poor functional outcome.[104 80,292] Many scores have been developed to measure the severity of SAH and these

are used to predict the likely outcome. The most commonly used are World Federation of Neurosurgical Societies (WFNS) score, Hunt and Hess scale, Glasgow Outcome Score (GOS)[112] and modified Fisher grade.[113] The population-based incidence studies included here did not use SAH-specific measures of severity due to the preponderance of ischaemic events in such studies. Therefore, we used harmonised measures across the studies focused mostly on the NIHSS. Poor neurological condition measured by a range of instruments on admission has been reported by others to be a strong predictor of mortality up to 1 year[293 280 294] and functional outcome.[295] Poor grade patients more often suffer from complications of SAH including rebleeding, hydrocephalus and delayed cerebral ischaemia (DCI).[116] Some investigators suggested that clinical grade or severity after neurological resuscitation in people with SAH predicts functional outcome.[295] Historically, poor grade SAH patients were not aggressively treated (e.g. aneurysm securement or ICU management) which may have increased their case-fatality rate but new investigations are confirming favourable outcomes in people with severe SAH. Further research to identify those SAH patient groups with severe bleeds that might benefit from active care or management are warranted. Better management strategies focused on preventing and managing complications in all patients, but particularly those with more severe bleeds, could help in improving the outcomes in patients of SAH.

Smoking independently predicted long-term mortality for SAH, as reported by a previous study.[276] Previously some studies showed that smoking was associated with better outcome after SAH. This was suggested to be a protective effect of nicotine, despite the younger age group, more existing comorbidities in smokers and the causal relationship between smoking and aneurysm formation and rupture.[79, 99] A recent study explained this paradox by survivorship bias and showed that smoking resulted in worse survival after SAH.[100] Smoking may be associated with a worse outcome because complications appear to occur more frequently in smokers after SAH, along with more smoking-related cardiovascular and pulmonary comorbidities that may affect outcome.[296] There is strong evidence of smoking associated with delayed cerebral ischaemia (DCI),[201] which is associated with short- and long-term mortality, as well as poorer functional outcome after SAH.[209, 297, 298] Identifying smoking in the risk factor profile of people with SAH is important as these patients may require closer monitoring and more aggressive physiological management. Assisting survivors to quit smoking could help improve longer-term survival of SAH and also prevent recurrence of SAH.[299]

We undertook this individual participant data meta-analysis due to a lack of large, high-quality datasets of people with SAH. There is a need for high-quality prospective studies of SAH to understand the needs for prevention, management, and outcomes in contemporary settings. We recommend that SAH should be part of ideal incidence population-based studies and national stroke registries. Information specific to SAH should be collected as we observed a lack of such data in existing studies. Important variables include the cause of SAH (e.g. aneurysmal or non-aneurysmal), risk factors, SAH-specific severity scales (e.g. WFNS or Hunt and Hess scales), type of treatment (conservative, clipping or coiling), long-term mortality, the functional outcome with more detailed assessments such as the Functional Independence Measure (FIM), return to work and other patient-reported outcome measures such as quality of life. Information on these variables could help us in identifying factors which could improve prevention or outcomes of SAH.

6.6.1 Limitations and strengths

To our knowledge, this is one of the largest studies ever to use data on SAH from high-quality population-based stroke incidence studies to determine the role of sex, and a range of other predictors, in mortality and poor functional outcome. The examination of outcomes at short and longer time-periods is also a strength as studies tend to only examine one or the other. Unlike the previous INSTRUCT study, this study included data set from Ludhiana (India) and Mashhad (Iran) that are low-income and middle-income countries respectively. This potentially makes these results more generalisable than the previous analyses which included more high-income countries.

There were some limitations of the current study. We included other causes of SAH in the study and could not specifically examine aSAH due to missing information on the cause of SAH. Information on functional outcome and deaths were recorded at different time periods, therefore, not all studies could be included together for the outcomes. The studies collected data over two decades, which might make pooling data problematic particularly given that outcomes have been reported to improve over that time frame.[294, 300] We did, however, adjust for the year of stroke in analyses to account for the change in management and outcomes over time. As noted earlier, the severity scores usually used in SAH (e.g. WFNS, Fisher Scale, Hunt and Hess) were not used in included studies because SAH accounts for a minority of cases in such studies (e.g. <10%) so protocols tend to use instruments appropriate for the more common ischaemic strokes (e.g. 80% of events). We, therefore, harmonised available stroke severity

scores but this results in a loss of information. There were also missing data on some important covariates including smoking status, alcohol intake which are likely not missing at random due to a larger proportion of missing data in people who died. We did, however, use multiple imputations to replace missing covariates using available data to maximise the sample size for analyses. There are unmeasured factors (e.g. hormonal and genetic) that were not measured in the studies included that might contribute to the outcomes after SAH. Also, a more general analysis not considering sex as the primary exposure might lead to different predictors of outcomes, with this a limitation of the model building used in this study.

6.6.2   Conclusion

In conclusion, we found that outcomes after SAH were independent of sex in this largest-ever international collaborative high-quality study for SAH. Other factors were found to predict survival and functional outcome including smoking, age and severity. Ensuring evidence-based management in smokers, the elderly and those with worse grade SAH could potentially reduce the poor outcomes that are common after SAH.

Appendix B: Sex differences in short and long-term mortality and functional outcome after subarachnoid haemorrhage (SAH) in INternational STRoke oUtComes sTudy (INSTRUCT)-A pooled analysis of the individual participant data

Search Strategy

Science direct

n=658 results found for pub-date > 2014 and

TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR "haemorrhage") AND TITLE ("mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends" OR "population-based" OR "community-based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance") .

Scopus

(n=1,525)

(TITLE ("population-based" OR "community based" OR "community" OR "epidemiology" OR "epidemiological" OR "incidence" OR "attack rates" OR "survey" OR "surveillance" OR "mortality" OR "morbidity" OR "fatality" OR "case fatality" OR "trends")) AND (TITLE ("stroke" OR "ischaemic stroke" OR "ischemic stroke" OR "intracerebral" OR "intraparenchymal" OR "subarachnoid" OR "haemorrhage" OR hemorrhage)) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , " ip ")) AND (LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2015)) AND (LIMIT-TO (LANGUAGE , "English "))

Pubmed

(n=1,952)

(((((stroke[Title] OR ischaemic stroke[Title] OR ischemic[Title] OR intracerebral[Title] OR intraparenchymal[Title] OR subarachnoid[Title] OR haemorrhage[Title] OR hemorrhage[Title])) AND ("2015/01/01"[PDat] : "2018/06/25"[PDat]))) AND (((population-based[Title] OR community-based[Title] OR community[Title] OR epidemiology[Title] OR epidemiological[Title] OR incidence[Title] OR attack rates[Title] OR survey[Title] OR surveillance[Title] OR mortality[Title] OR morbidity[Title] OR fatality[Title] OR case fatality[Title] OR trends[Title])) AND ("2015/01/01"[PDat] : "2018/12/31"[PDat])) AND

(("2015/01/01"[PDat] : "2018/06/25"[PDat])) AND (("2015/01/01"[PDat] : "2018/06/25"[PDat]) AND Humans[Mesh])

Chapter 7: Discussion

There is limited literature available on sex differences in the risk factors and outcomes of aSAH, unlike ischaemic stroke. In this thesis, I extensively examined sex differences in aSAH including, the risk factors in a systematic review and the outcomes after aSAH using two datasets. Regarding risk factors for aSAH, the rationale of this research was that previous reviews were conducted more than a decade ago with sex differences explored as a part of sub-analysis in studies that included non-aneurysmal causes of SAH. The rationale for examining sex differences in outcomes after aSAH was that very few studies have examined outcomes after aSAH with a specific focus on sex, particularly at long-term. I found no difference by sex in common risk factors for aSAH, but genetic risk factors were identified as a possible explanation of sex differences in incidence. Women-specific risk factors could explain why aneurysm formation and its rupture might be more common in the female sex. Few differences by sex were detected in the outcomes examined in this thesis. Although I had postulated that the reasons why sex differences were not found could have been due to methodological issues with previous studies including the methods of analysis, this did not appear to be the case. However, some risk factors and neurological complications were found to be more common in women than men. The results from this thesis will not only add to the body of evidence regarding sex differences in aSAH but also highlight the measures that might be necessary to improve aSAH management and outcome in general. This chapter provides a general summary and discussion of the findings as well as future directions for research and potential implications of the findings.

7.1 Summary of findings

7.1.1 Sex differences in risk factors and greater incidence in women

Examining sex differences in the risk factors for aSAH was one of the research questions of this thesis since aSAH is more common in women than men (See **Research Questions** in Introduction chapter). I aimed to examine if there were sex differences in the risk factors for aSAH in the existing literature and if they might explain the greater incidence in women compared to men. In **Chapter 3**, in a systematic review and meta-analysis, I reported that women had a greater risk of aSAH compared to men. Women-specific risk factors like early age of menarche, later age of pregnancy and nulligravidity were associated with an increased risk of aSAH in women; and among genetic variations, clotting factor XIII and 9p21 polymorphism increased the risk of aSAH in women than in men. Alcohol, high alkaline

aminotransferase levels (ALT), endothelial nitric oxide synthase gene (NOS3) 27-bp-VNTR b/b genotype polymorphism increased the risk of aSAH in men compared to women. Known risk factors such as smoking, hypertension, increased systolic blood pressure, family history of aSAH and age were associated with a similar increased risk of aSAH in both sexes. In conclusion, not many risk factors for aSAH differed between the sexes despite the difference in incidence between men and women. Further studies are required regarding women-specific risk factors and genetic variations identified in the review. Meanwhile, a re-analysis of existing studies on risk factors for aSAH which have not reported sex differences could be helpful.

7.1.2   Sex differences in short and long-term outcomes

Examining sex differences in the outcomes after aSAH was the second research question of this thesis (See section **Research Questions).** I aimed to examine if there were sex differences in discharge destination, survival or poor functional outcomes in the short and long-term after aSAH. This was explored across three chapters of this thesis using two datasets. In **Chapter 4,** using a retrospective cohort study of cases of aSAH from two hospital networks, (the REDDISH study), I found that women were older, had a history of hypertension and less often smoked than men. Women suffered more from neurological complications including delayed cerebral ischaemia (DCI) and hydrocephalus than men. They had a marginally greater risk of poor short-term outcomes which included in-hospital death and discharge to rehabilitation, although these differences were not statistically different. There was evidence that the somewhat elevated worse outcome in women was explained by age, hypertension history, DCI, and hydrocephalus. When matched on pre-stroke confounders using inverse probability of treatment weighting including age, hypertension history and smoking status, the results were consistent with adjusted analysis. The slightly poorer outcome in women than men at discharge was partially attributable to pre-stroke confounders and neurological complications. Prevention of risk factors and improvements in managing complications could improve outcomes after aSAH.

In **Chapter 5**, using a retrospective cohort study of cases of aSAH from two hospital networks, (the REDDISH study) it was observed that 74% of the patients survived up to 1 year, with no difference by sex noted. There was no difference in the causes of death between men and women after aSAH. In a model including optimal care, age, severity scores, comorbidities, DCI, and hospital network no association of sex was detected for 1-year mortality. Around 59% of aSAH patients received optimal care. It was also noted that comparatively younger patients

and those with a less severe stroke were more likely to receive active management while those who were older or with severe stroke were more likely to be given comfort measures only. The severity of the stroke, age, type of management influenced receipt of optimal care with the relationship of these variables and outcomes very complex. In conclusion, long-term outcome was independent of sex but predicted by age, severity scores, comorbidities, and optimal care in patients with aSAH.

In **Chapter 6,** using data from an individual participant data analysis of people with aSAH from 13 ideal stroke incidence studies around the world (INternational STRoke oUtComes sTudy – INSTRUCT) I explored sex differences in short and long-term mortality and functional outcome following SAH. A limitation of this study, due to the historical nature of some of the data, was that the data were not specific to aneurysmal causes of SAH. I found that there were no significant sex differences for mortality at multiple time points. Mortality at 1 month was predicted by age and stroke severity, at 1 year by age, stroke severity, and current smoking, and at 5 years by age, stroke severity and current smoking. Regarding functional outcomes, poor outcome was not different by sex but was independently associated with age at 1 month, stroke severity at 1 year. Sex was not a predictor of poor outcomes after SAH. Smoking, a risk factor related to the incidence of aSAH made outcomes worse. Better management strategies in older patients and those with severe strokes could improve outcomes after SAH.

In the above studies, no differences by sex was detected but improvement in prevention and management of aSAH could improve the outcomes overall.

7.1.3   Sex differences in evidence-based processes of care

Another research question was to examine if there were sex differences in the receipt of evidence-based care after aSAH (See section **Research Questions).** This was examined using the REDDISH dataset in **Chapter 5**. Individual indicators including antihypertensives if systolic blood pressure (SBP)≥160mmHg, nimodipine and aneurysm treatment and 'optimal care' (e.g. receiving all eligible processes of care) were examined between men and women but no difference by sex was noted. There were no differences between men and women in receipt of aneurysm treatment within 72 hrs and receipt of nimodipine and antihypertensives within 24 hrs. In conclusion, the receipt of evidence-based care was similar in both sexes. However, around 40% of the cohort was deprived of optimal care. More research is needed on measuring the adherence to the guidelines and to understand the gaps in the provision of care after aSAH.

7.1.4   Factors contributing to sex differences in the outcomes after aSAH

I also examined the contribution of factors including pre-event factors like age, hypertension and smoking status or clinical factors like complications or aneurysm characteristics to the sex differences in short and long-term outcomes after aSAH (See section **Research Questions**). As discussed, there were limited sex differences observed in the outcomes in the short or long-term after aSAH. However, some factors were observed to be different by sex and were also associated with poor outcomes. The factors identified were age, history of hypertension, current smoking, DCI, and hydrocephalus. These factors could be important as some benefit from consideration of sex-specific management and are discussed below.

7.1.4.1 Age

In this thesis, it was observed that women were older than men after aSAH similar to findings of other studies,[64, 65, 69, 88] and greater age, predicted poor outcomes in my studies. Increasing age is associated with comorbidities[243, 283] which could worsen the stroke. Older patients are also more prone to lethal complications after aSAH like shunt-dependent hydrocephalus[110, 286] and rebleeding[287, 288] leading to worse outcomes. It is important to note that the majority of men and women suffering from aSAH are in a younger age group usually between 45-55 compared to ischaemic stroke, which is common after the age of 70 and above.[301] It has been reported that older patients with severe aSAH are more likely to be placed on comfort measures due to unfavourable outcomes.[236] Recent studies have shown that uncompromised quality of care in older patients could improve the outcomes after aSAH,[238,243] therefore, there may be a need to consider more aggressive management plans for more older patients with aSAH, as clinically appropriate.

7.1.4.2 Vascular risk factors

There were some differences in vascular risk factors between men and women who had aSAH. It was observed that women more often had a history of hypertension partially attributable to their relatively older age compared to men, and it was associated with poor outcomes. Higher blood pressure could be a risk for complications after aSAH including rebleeding[302] and cerebral infarction,[219, 303] and is associated with risk of sudden death after aSAH.[217] As high blood pressure may be an underlying cause of death or disability after aSAH, better management of blood pressure in hypertensive patients could be useful for better outcomes.

More men were current smokers than women as per findings in the studies of this thesis and outcomes were worse in current smokers. Smoking, like hypertension, adds to the poor risk profile of aSAH patients potentially contributing to sudden death.[217] There is evidence of DCI, a fatal neurological complication, being more common in smokers.[98] This is proposed to be due to the vasoconstrictor endothelin, which is elevated in smokers, causing arterial spasm in cerebral arteries after SAH.[304] Better preventive measures like counselling about the cessation of smoking and strategies to educate about tobacco use could be an effective measure to prevent aSAH. Consideration of smoking status in terms of management to prevent complications like DCI may be an avenue for further research.

7.1.4.3 Neurological complications

It was observed that the neurological complications of DCI and hydrocephalus were more common in women compared to men and were associated with poor outcomes. Sex differences have been observed in some previous studies in DCI.[88, 98] Regarding hydrocephalus, some studies showed that women were more affected by this complication than men[110, 305], and age, poor-grade SAH, posterior location aneurysm, vasospasm, higher bicaudate index[110, 305-308] could be contributing to its occurrence. In short, more women suffered from neurological complications than men, which likely means a longer hospital stay for the treatment of these complications and extra costs of care, although I did not examine these in my study. There is a need for more research to understand the role of sex in the occurrence and pathophysiology of these complications. This may assist in preventing these complications in women, but also men with aSAH, to improve the outcomes.

7.2   Future directions

7.2.1   Studies on women-specific risk factors for aSAH

I identified several women-specific risk factors for aSAH including the age of menarche, age of pregnancy, gravidity, parity, use of oral contraceptive pills (OCPs), use of hormone replacement therapy (HRT) and age of menopause. These hormonal factors could potentially explain the cause of greater incidence of aSAH in women than men, but the number of studies that examined aSAH and these risk factors are very few. Therefore, there is a need for more evidence regarding the association of these factors with the risk of aSAH. Conducting prospectively designed population-based studies or case control studies in women to examine the role of the relationship of hormonal variations throughout the life of women and the

occurrence of aSAH could provide answers to understand a greater risk in women. There are many existing studies including the Million Women Study, Nurses' Health Study, Midlife Women's Health study, Australian Longitudinal Study of Women's Health focused on women that have data on various hormonal and reproductive factors. Data linkage to these existing data sets to identify fatal and non-fatal cases of aSAH might be helpful to find information on the association of women-specific risk factors recorded in these studies and the occurrence of aSAH. There might be a limitation of the number of cases of aSAH in these studies as it is rare, but being prospectively designed population-based studies individual participant data could be pooled from different studies to increase the power of cohort of aSAH. More high-quality longitudinal observational or case control studies in women should be conducted for answering the questions around women-specific risk factors and aSAH.

7.2.2 Intervention studies targeting women-specific risk factors

Given these findings, hormonal therapies may help reduce aneurysmal rupture in women but also potentially in men. Aneurysmal formation and rupture have been linked to estrogen deficiency in women[170] resulting in the incidence of aSAH being common around menopause. Studies have shown controversial results regarding the use of HRT in postmenopausal women,[170, 176, 309] while animal studies have shown promising results for selective estrogen receptor modulators in the prevention of aSAH.[310] Clinical intervention studies could be conducted in women with diagnosed unruptured intracranial aneurysm (UIA) to examine the effect of exogenous hormonal medications such as OCPs or HRT and other physiological factors (parity, number of pregnancies, age of menarche) with outcomes that may include aneurysm growth or estimated risk of rupture. This might help understand the pathophysiological role of hormonal factors and identify potential therapeutic interventions in cerebral aneurysm formation, growth, and rupture which may open doors for the use of hormonal medications in prevention of aSAH in women.

7.2.3 Improvements in epidemiological studies of aSAH

Efforts should be made so that large population-based studies and stroke registries include aSAH. The low number of cases of aSAH in population-based stroke incidence studies limits the ability to do detailed analyses. I found that in existing incidence studies besides a small number of SAH cases, there was a lot of missing data for SAH patients regarding risk factors and outcomes. The low number of cases of aSAH in stroke incidence studies in most population-based studies limits the ability to do detailed analyses. There is a need to improve

the recording of risk factor profiles of aSAH patients in such studies. I noted that details of common factors like hypertension history, past or current smoking and alcohol intake, family history or use of hormonal therapy were usually missing in the large prospective studies. These data were not collected partly because these were studies based on all types of stroke, which are mostly ischaemic events, whereas the important risk factors for aSAH may be different. Further, the high early death in people with aSAH can make collecting such data difficult in prospective studies. Data collection in these studies could be improved by adding risk factors and measures specific to SAH, for example, severity scores which are different for SAH than ischaemic stroke. Also, follow-up of SAH patients should be completed at the specified time (at 1 year or 5 years) as per the protocol of the studies to overcome missing information on outcomes. The above measures could be crucial in examining sex differences robustly, identifying the causative factors of worse outcomes and improving the sex-specific and overall care.

aSAH is also not a part of national stroke registries like the Australian Stroke Clinical Registry (AuSCR),[311] in which data is collected regarding evidence-based care and outcomes. Funding could be a constraint for not creating a registry specific to aSAH due to a lower number of cases. It is, therefore, preferable to include aSAH in large stroke registries. This might require a few additions to the list of variables, which may include a family history of aSAH, severity scores (WFNS, modified Fisher score), and use of nimodipine, and aneurysm treatment (coiling/clipping) as indicators of care. These efforts could prove fruitful in gathering information regarding SAH on a larger scale without creating a separate registry for aSAH. In addition, differences by sex in different aspects including risk factors, management and outcomes could be examined nationwide using these registries.

7.2.4 Patient-centred outcomes

The overall conclusion of this thesis is that there were few sex differences in survival, discharge destination or functional outcome after aSAH. In chapter 4-6, outcomes were examined and compared between the sexes at short and long-term including death and poor functional outcomes after discharge, up to 1 year and 5 years. It is to be noted that we included one large data set with retrospective data and pooled ideal population-based prospective stroke studies for the analyses. The outcomes recorded in these studies were 'hard' clinical endpoints, e.g. deceased or not and discharged to rehabilitation or not, largely because of the retrospective nature of the study. These studies did not record for patient-centred outcomes for aSAH or

SAH patients such as quality of life, the Functional Independence Measure (FIM), return to work or gait speed. Previously a few studies of aSAH have reported these outcomes with sex differences noted but these studies had limitations, with a substantial loss to follow-up.[77, 78, 81] Examination of sex differences is crucial regarding these outcomes because they align more closely with what is important to the patient and their family. Unfortunately, the existing stroke incidence studies did not gather quality of life outcomes, which could be attributed to a lower volume of cases. There is, therefore, a need to record patient-related outcomes in SAH patients in these high-quality studies as this will help with improving the quality of life in patients of aSAH. It is possible that if a broader range of outcomes that better characterise peoples' lives after aSAH was examined then sex differences would be seen. Given the predominance of traditional gender roles in society, it possible that there are different impacts on participation (e.g. social and family roles) and quality of life for a woman suffering an aSAH compared a man but the lack of in-depth studies makes it difficult to fully explore these differences.

7.2.5 Understanding the pathophysiology of neurological complications in both sexes

It was observed that an association was detected between sex and neurological complications including DCI and hydrocephalus and this was independent of age and severity of stroke. More studies are needed to examine the pathophysiology of these complications to understand why there are sex differences. This may help in devising ways to prevent or manage these complications more effectively.

To improve the prevention of DCI in women and men, the role of sex in the development of DCI should be explored. This could further help in redefining prediction scales and taking effective sex-specific measures to prevent DCI. Similar efforts could also be made for preventing hydrocephalus in women and men. DCI is treated by using endovascular therapy or intra-arterial vasodilators and, hydrocephalus is managed by ventriculostomy and ventriculoperitoneal shunt (VPS). As women suffer more from these complications, this likely lengthens their stay at the hospital, adds expense to treatment costs and increases the chances for rehabilitation as a part of the recovery process. Therefore, understanding the role of sex in the occurrence of complications might help plan strategies specific to women to overcome further neurological damage, but would likely have benefits for both genders. There has been some pre-clinical research in animal models that favours the role of hormones, for example, estradiol improves the vasospasm, one of the mechanisms, resulting in DCI.[312, 313] However, more clinical trials on human subjects are necessary to examine how these hormones might

affect cerebral vascular circulation in patients after aSAH and possibilities of using these as a therapeutic intervention for DCI could be explored.[314]

7.2.6 Randomised control trials (RCTs) for the management of UIA

The prevalence of UIAs is more prevalent in women than men .[44] There is some evidence that women with certain risk factors have a higher risk of rupture than men with the same risk factor. For example, It was shown in a study that life-time risk of rupture in women who are current smokers with UIA $\geq$ 7mm was remarkably increased compared to men.[315] UIA are typically monitored with regular neuroimaging with the option to advance to prophylactically treating the aneurysm if it becomes at a higher risk of rupture potentially leading to devastating aSAH. The current clinical practice is to perform aneurysm treatment depending on the growth of the aneurysm with these decisions based on evidence from RCTs and observational studies of aSAH.[44, 316] There is, however, a lack of evidence from RCTs regarding measures to be taken for managing UIA. An important consideration is that there is around 6%-10% likelihood of poor neurological outcome after preventive repair of UIA compared to the mean 5-year risk of rupture which is 3.4%.[316] There is a trial for UIA being conducted[317] to compare the outcomes of coiling and clipping over the long-term and findings could be useful for the provision of best-practice management for patients with UIA and prevention of aSAH. There is recent evidence from a cohort study that people taking aspirin and that have well-controlled blood pressure have lower aneurysm growth than those not taking aspirin or with poorly controlled blood pressure.[318] Further exploration of the use of non-surgical interventions to manage UIA using randomised controlled trials with enough power to examine sex differences are needed. Similarly, if evidence were found in the cohort study approach suggested above (e.g. with the Million Women Study or similar) or case control studies that certain hormonal factors were associated with aneurysm growth or aSAH then potential targets could also be explored in a clinical trial design, for example using different types of hormonal contraceptives. Recently, a decline in the incidence of aSAH has been noted over a long-term by authors of different studies.[319-321] Some attributed this to control of modifiable risk factors (e.g. smoking)[319, 321] while some suggested that the treatment of UIA could be contributing to this decline.[320] However, more studies are needed to specifically explore association of UIA management and decrease in the incidence of aSAH with an account of sex.

7.3 Policy and practice implications

7.3.1 Provision of evidence-based care

There is a need to provide patients with aSAH with better care based on current evidence from RCTs and clinical studies. Results of recent trials suggest that there is a need to revise the guidelines. For example, there is emerging evidence of a reduction in the rates of DCI by using goal-directed haemodynamic therapy (GDHT)[322] compared to standard clinical care in aSAH. This includes advanced haemodynamic monitoring, fluid management and monitoring of various cardiovascular parameters including mean arterial pressure, global-end diastolic index, cardiac index, and extravascular lung index. However, in a recent RCT, other investigators reported some adverse effects regarding the use of induced hypertension in patients of aSAH with DCI,[323] therefore careful review of all evidence would be required before reconsideration of the guidelines. In another RCT, a new medication (Cilostazol) has been tested for DCI prevention with better outcomes and with lesser adverse effects.[324] There has also been recommendations for improving endovascular coiling techniques that could improve the outcomes after aSAH.[325] In general, the guidelines[119, 120] for managing aSAH are almost a decade old and need to be updated according to the current results from different types of evidence. In Australia, there is potential to add management of SAH into clinical guidelines, such as those developed by the Stroke Foundation.[326]

7.3.2 Enhancing quality of care

It was observed in this thesis that most patients with aSAH did not receive care as per guidelines. This was also noted in a previous study,[327] however, the measures in the previous study were general to stroke and not specific to aSAH. Potential targets may include educating the clinicians and nurses in the ED, radiology services, neurosurgical units and intensive care units regarding the management of aSAH. Audit, feedbacks, quality of care registries could be used to monitor the adherence to guidelines and build capacity to deliver the best quality of care, as used successfully for ischaemic stroke.[242] There are in-hospital programmes like 'Get With The Guidelines' program in the USA[328] created to improve quality of care and provision of best-practice guidelines for acute ischaemic stroke patients. Stroke care measures in this program cover various aspects of ischaemic stroke but for haemorrhagic stroke, the only indicator is smoking cessation. There are no such existing programmes for SAH to measure adherence to guidelines. In Australia, SAH is not a part of the national stroke registry, that is the Australian Stroke Clinical Registry (AuSCR).[311] To measure nationwide adherence to guidelines in SAH

treatment, it is recommended that SAH should be added to AuSCR. There are likely to be requirements for SAH specific data through a separate module. Indicators specific to aSAH treatment may include receipt of nimodipine and aneurysm treatment (coiling/clipping). There would be a requirement for collaboration with a wide range of clinical groups that manage aSAH including neurosurgeons, interventional neuroradiologists, intensive care physicians, emergency department physicians, as well as nursing staff across these areas. This would help in creating the first prospective national registry of SAH cases that will also assist in monitoring and enhancing the quality of care in SAH patients.

Provision of mobile health and telemedicine[329, 330] could also be a road towards better provision of care in aSAH patients especially, in rural areas. People with aSAH in regional areas may access specialist consultation quickly with reduction in delays in diagnosis and early management. The aspects of delays in the provision of care and ambulance bypass in aSAH management are important to address to the enhance quality of care. This has been explored in detail in the 'time to treatment' aspect of REDDISH data, which is a broader study and hence was not examined in the current thesis.

7.3.3 Prevention guidelines for women

It is noted that guidelines mentioned female sex as a risk factor for aSAH[119] and also for UIA.[44] At present these guidelines do not address specific preventive measures in women. There are separate guidelines for the prevention of ischaemic stroke[28] or heart diseases[29] in women and I would recommend the same for aSAH and UIA. The sex-specific guidelines could be helpful to identify and manage the common risk factors for aSAH by recommending preventive measures including smoking cessation or monitoring of blood pressure and consequently lowering the incidence of aSAH in women. In my thesis, it was found that post-SAH complications including DCI and hydrocephalus were more common in women. With development of further evidence regarding the reasons for sex differences in DCI and hydrocephalus after aSAH, the guidelines' recommendations could also include sex-specific preventive measures and interventions regarding these complications.

7.3.4 Prevention programmes in high-risk groups

Prevention programmes could be carried out for public awareness about aSAH especially in high-risk groups which may include post-menopausal women, people with hypertension, smokers, and those with a family history of aSAH. People can be educated through these programmes about common symptoms of aSAH including severe and sudden headache, neck

stiffness, nausea and vomiting, focal neurological deficits (e.g. hearing and vision problems) and loss of consciousness. These programmes may also education about 'lifestyle interventions' as preventive measures to manage the risk factors to reduce aSAH risk. For example, decreasing salt, maintaining a balanced food intake and exercise can avoid high blood pressure,[331] and cessation of smoking can reduce the occurrence of cardiovascular diseases including stroke.[332] 'Screening and therapeutic interventions' for high-risk groups which many include treatment and monitoring of hypertensive patients during routine visits to hospitals and clinics, and rigorous follow-up of those with a family history of aSAH. 'Mass media approach' could help provide education about aSAH using TV, posters on public transport, internet, or newspapers, although as aSAH is rare this approach may be of lower value. Educating about aSAH and its risk factors in the community, teaching institutes and workplaces might help[333] and specifically making women aware of the aSAH visiting for routine check-ups. Legislative changes for example introducing better anti-smoking policies to restrict tobacco use which might not only help to reduce aSAH but also other cardiovascular diseases.[334] These preventive measures could be introduced on a large scale by adding SAH as a subcategory in awareness programmes for stroke[335] including mobile phone applications.[336]

7.4   Conclusion

In conclusion, despite no detectable sex differences in the outcomes of interest, women were still more affected by aSAH than men due to the absolute number of events occurring. They were overrepresented in aSAH cohorts, were older, hypertensive, and more often had neurological complications after aSAH than men. Hence, more women underwent admission for aSAH treatment and additional management for complications, increasing the burden of the disease. There is a need to conduct more high-quality large multicentre studies to examine sex differences in functional and patient-related outcomes in the longer-term after aSAH. This should include national stroke registries and follow up of SAH cases in ideal stroke population-based studies. There is a potential for advances in this field by enhancing preventive strategies and improving the quality of care to reduce the incidence and improve the outcomes of aSAH.

Appendix C: Publication 1

Review Article

Sex differences in risk factors for aneurysmal subarachnoid haemorrhage: Systematic review and meta-analysis

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ABSTRACT

Background: Aneurysmal subarachnoid haemorrhage (aSAH) disproportionally affects women. We conducted a systematic review and meta-analysis to explore sex differences in aSAH risk factors.
Methods: Case-control/cohort studies were searched to November 2017 with sex-specific risk factors for aSAH. Meta-analysis was performed when a risk factor was reported in ≥2 studies.
Results: Of 31 studies, 22 were eligible for meta-analysis. Female sex was associated with greater odds of aSAH ($HR_{adjusted}$ 1.90 [1.47–2.46]. There was no detectable difference between the sexes for hypertension ($OR_{adjusted}$: men 3.13 [2.26–4.34]; women 3.65 [2.87–4.63], $p = .18$), smoking ($OR_{adjusted}$: men 2.96 [1.68–5.21]; women 3.11 [1.21–7.97], $p = .95$), aSAH family history, systolic blood pressure, age and some genetic variations. Alcohol ($OR_{adjusted}$: men 1.50 [1.04–2.17]; women 0.83 [0.48–1.45], $p = .003$), high alanine aminotransferase levels, and some gene variants increased the risk of aSAH in men. Reproductive factors, divorce and some genetic variations increased the risk in women. High aspartate aminotransferase levels in men and, diabetes ($OR_{adjusted}$: men 0.57 [0.32–1.01]; women 0.24 [0.13–0.43], $p = .01$) and parity in women reduced aSAH risk.
Conclusion: We recommend sex-specific re-analysis of existing studies of aSAH risk factors. Known aSAH risk factors (hypertension, smoking and alcohol consumption) should be targeted to prevent aSAH in men and women.

Registration PROSPERO (ID: CRD42018091521).

1. Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) occurs more often in women than in men [1,2] but the reasons for this are unclear. SAH results from the rupture of an aneurysm in approximately 85% of cases [3]. Of note, the prevalence of unruptured intracranial aneurysms is higher in women compared to men (4.4 vs 2.5%) [4] consequently increasing the risk of rupture. The risk factors for aSAH are likely to be distinct from other causes of SAH, but few studies have been conducted to explore sex differences in risk factors for aSAH. In a systematic review on risk factors for SAH, Tiunissen et al. did not detect sex differences in alcohol consumption, cigarette smoking and hypertension [5]. Feigin et al. conducted an updated systematic review of SAH, and

reported that hypertension and alcohol intake were more hazardous in women while hypercholesterolemia reduced the risk of SAH in men, although none of these risk factors were statistically different between women and men [6]. These reviews included studies with varied designs (e.g. clinical trials, case-crossover studies, etc), were not focussed on sex differences, and included only a limited number of risk factors. In addition, these reviews did not include examination of sex differences in genes associated with the risk of aSAH.

Our aim was to conduct a comprehensive review of sex differences in risk factors for aSAH to explore the reasons for the greater incidence in women than men.
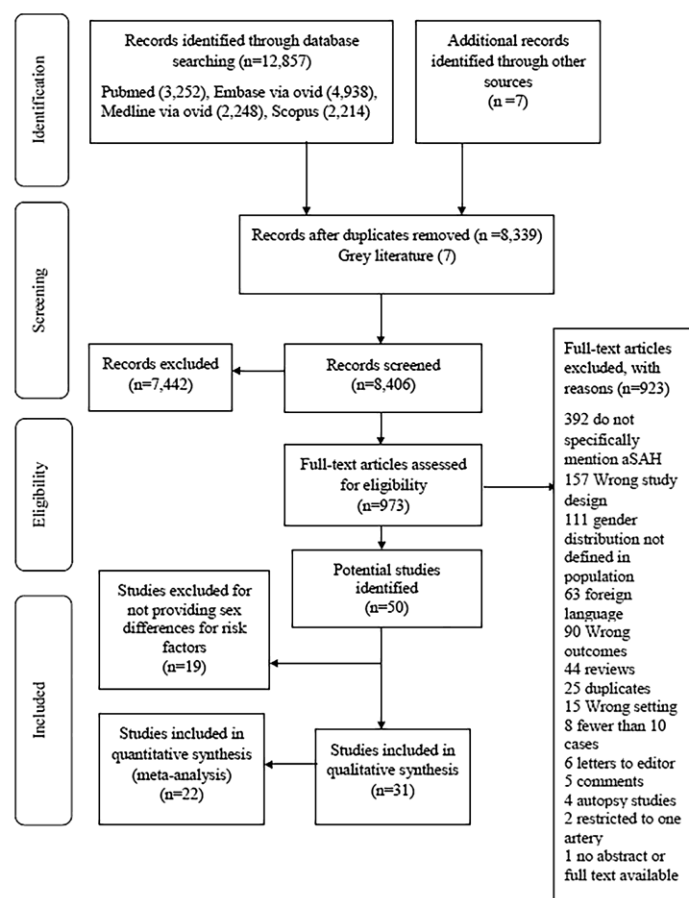
Fig 1. Prisma flow chart for the selection of the studies for systematic review and meta-analysis.

2. Methods

2.1. Literature sources and search strategy

Pubmed, Scopus, Medline via Ovid and Embase via Ovid were searched from inception to Nov 27, 2017. The Appendix A provides the full search strategy. Keywords and medical subject headings used for searching the databases included "sex characteristics", "sex difference", "gender difference", "sex based", "sex distribution", "sexual dimorphism" AND "aneurysmal subarachnoid haemorrhage", "ruptured cerebral aneurysm", "ruptured intracranial aneurysm", "ruptured brain aneurysm" AND "risk factors". The review was registered with PROSPERO (ID: CRD42018091521). Studies focused specifically on cohorts of women or case-control studies with women only were examined.

2.2. Study screening for title and abstract

Two reviewers (SR and BWS) screened titles and abstracts based on the following inclusion criteria: (1) cohort, case-control, cross-sectional, case series or case-reports at least 10 cases, (2) provided details of

stroke subtypes or subarachnoid haemorrhage and risk factors, (3) mentioned sex differences in risk factors or were women specific studies but with risk factors not limited to only women like smoking or hypertension (4) were published in English. Studies were excluded if they were 1) animal-based, experimental, autopsy series, or included fewer than 10 patients, or 2) included non-aneurysmal SAH, either on its own or as a combined category with aSAH.

2.3. Full text screening

For full-text screening, a study was included when: (1) It was a cohort or case-control study, (2) included aneurysmal subarachnoid haemorrhage, had criteria indicating that history and CT findings were highly suggestive of aneurysmal origin, and did not provide evidence of inclusion of SAH other than aneurysmal rupture, (3) provided effect estimates with 95% CI or raw data to calculate these, included risk factors that were stratified by sex, or included an interaction term between sex and risk factors for aSAH.

2.4. Risk of bias and methodological quality assessment

Two independent reviewers (SR and MD) used Newcastle-Ottawa Quality Assessment Scale [7] for case-control and cohort studies to assign level of quality to each study. This scale has a range from 0 to 9 and was modified for this review (See Appendix B, Supplementary Methods, Appendix C Supplementary Tables C.1–C.4). Any conflict between the two reviewers was resolved by discussion.

2.5. Data extraction

Reviewers (SR and MD) independently extracted predefined data items (see Appendix B Supplementary methods). If a study provided more than one adjusted estimate, the fully adjusted estimate was extracted. If two or more studies provided effect estimates for a given risk factor, it was included in the meta-analysis.

2.6. Data analysis

Crude and adjusted odds ratios (OR), risk ratios (RR), or hazard ratios (HR) were reported for different risk factors for aSAH for men and women. Random-effects meta-analysis was used to pool estimates by approximating OR and RR for available studies. Subgroup analysis was performed by comparing the pooled results of similar studies for a risk factor in men and women. We included studies in the analysis in which aneurysm was further confirmed by angiography, MRA (Magnetic Resonance Imaging), DSA (Digital Subtraction Angiography), during surgery or at autopsy and, performed sensitivity analysis for the studies which did not mention gold standard imaging methods or techniques for confirmation of the aneurysm. The mvmeta [8] command was used to conduct multivariate meta-analysis to test statistical significance of sex difference for the risk factors in those studies with stratified estimates. We also performed meta-regression between regions of low and high incidence of aSAH. Data analysis was conducted using Stata 15 (StataCorp LLC, Texas, USA). Begg's test was used to assess publication bias and p-value $< .05$ was considered as significant.

3. Results

From 12,864 records, 50 potential studies including two abstracts (case-control studies = 42, cohort studies = 8) on risk factors for aSAH were identified (Fig. 1). Among 31 studies of sex differences in aSAH, two of which were abstracts (case-control studies = 27, cohort studies = 4), there were a total of 8611 cases in 27 case-control ($n = 7726$) and 4 cohort ($n = 885$) from 15 countries. We could not include 19 studies (case-control studies = 15, cohort studies = 4) as no sex specific results were reported by the authors. Most of the studies were from Japan ($n = 6$) and Sweden ($n = 6$), followed by Norway ($n = 3$), and the United States of America ($n = 3$). All case-control studies were of high quality, with score ≥ 6 except one, which was an abstract. Three out of four cohort studies were of high quality with scores ≥ 6. No evidence of publication bias was found.

3.1. Risk factors

A summary of all the risk factors across the studies is provided in Tables 1, 2 and 3.

3.1.1. Female sex

The association between sex and the risk/odds of aSAH was examined in eight case-control and two cohort studies (OR$_{crude}$ range: 0.64–2.30, OR$_{adjusted}$ range: 0.69–2.13 for case-control studies; HR$_{crude}$ 1.7 in one cohort study, HR$_{adjusted}$ 1.9 in two cohort studies). See Appendix C Supplementary Table C.5, Appendix D Supplementary Fig. D.1. Crude estimates were reported in three case-control studies, [9–11]

Table 1
Risk factors identified from cohort and case-control studies.

Risk factors	Number of cohort studies studies		Number of case-control studies	
Women specific	Number of studies	Number of cases (% women)	Number of studies	Number of cases (% women)
Female sex	2	160(67)[a]	7	2239 (63)[a]
Age at menarche	1	76	1	124
Parity	1	78	2	405
Age at first pregnancy			1	124
Menstrual cycle regularity			1	124
Menopause status	1	79	1	124
Age at first child birth			1	124
Gravidity			1	124
Marital status	1	185		
HT use	1	58		
aSAH predilection area	1	44		
OCPs use	1	N/A	1	4
Common in both sexes				
Smoking	1	120(66)	12	1631(48)[b]
Blood Pressure/SBP	1/1	89(48)/120(66)	7	811(61)[b]
Hypercholesterolemia			3	283(74)
Hypertriglyceridemia			1	7(71)
Diabetes Mellitus			3	62(51)
Alcohol intake	1	119(66)	5	649(25)[b]
Liver Disease			1	18(33)
CAD			2	114(71)
Family History	1	37(73)	1	29(62)
Migraine			1	1
Stress (Work or children related)			1	380(66)
AST			1	38(60)
ALT			1	33(42)
UN			1	54(55)
ADAMST13 polymorphism			1	183(74)
GpIIIa A1/A2 polymorphism			1	201(44)
FXIII VARIANT H2 & H3			1	183(74)
Genotype II of the ACE gene			1	90(63)
NOS3 27-bp-VNTR b/b genotype			1	333(70)
Genetic variation on 9p21			1	183(74)
Age	1	120(66)	1	120 (66)
Cold temperature			1	1(N/A)
Total = 34				

ADAMST13: A Disintegrin-like and Metalloprotease with Thrombospondin Type1 Motif, 13, ALT: Alkaline aminotransferase, AST: Aspartate aminotransferase, Gp: Glycoprotein, HT: Hormonal Therapy, FXIII; clotting factor XIII, ACE; Angiotensin Converting Enzyme, NOS; Nitric Oxide synthase, OCPs: Oral contraceptives, UN: Urea Nitrogen, VNTR: variable number tandem repeat.
[a] %age of women against men.
[b] %age for women is average of sex specific data provided by some of the studies.

and one cohort study [12] while adjusted estimates were reported in six case-control studies [9,13–17] and two cohort studies [12,18]. Sensitivity analysis was performed for the studies that did not use gold standard imaging techniques for aneurysm confirmation, but results did not vary after excluding them.

3.1.2. Women-specific risk factors

We observed women-specific risk factors for aSAH across different studies. See Appendix C Supplementary Table C.6. In two studies, authors examined risk or odds of aSAH associated with age at menarche. Menarche at age < 13 years was a risk factor for aSAH in multivariable analysis in one case-control study [19]. In a cohort study, compared to

Table 2
Case-control studies: Risk factors in included studies.

Study	Year	Country	Study years	Cases of aSAH	Risk factors	Assessment of risk factors
Adamski et al. [13]	2009	Poland (Kraków)	2001–2007	288	GpIIIa A1/A2 polymorphism, Female sex	PCR, RFLP
Anderson et al. [30]	2004	Australia (Adelaide, Hobart, and Perth) & New Zealand (Auckland)	1995–1998	330	Past, current and never smoking	Structured in person interview with standardized questionnaire & Medical records
Bell & Symon [29]	1979	United Kingdom (London)	1965–1978	208	Smoking	Hospital records verified by postal questionnaire
Can et al. [9]	2017	United States of America (Boston)	1990–2016	1302	Female sex	Medical records
Canhao et al. [24]	1994	Portugal (Lisbon)	1985–1990	141	HTN, Tobacco use, DM, High cholesterol High triglycerides	In person interview & measurement of Blood pressure, fasting glucose
de Wilde et al. [38]	2013	Netherlands (Utrecht)	not given	490	Stress related events in life (work and children)	Self-report
Galst et al. [21]a	2004	Sweden	1973–1997	281	Parity, Smoking prior to first child birth	Birth, in-patient & cause of death registries
Hanson et al. [37]	2013	Sweden (Gothenburg)	not given	183	Genetic variation at ADAMTS13	Genotyping
Inagawa [31]	2005	Japan (Izumo)	1980–1998	247	HTN, DM, CAD, Liver disease, High cholesterol, Current regular & former smoking, Daily drinker, AST level > 40iu/l, ALT level > 35iu/l & Urea Nitrogen level. > 20 mg/dl	Medical history and serum levels
Inagawa [32]	2010	Japan (Izumo)	1981–2005	858	HTN, DM, CAD, High cholesterol, Current, regular & former smoking, Daily drinker	Medical history (disorders and lipid lowering medication), and serum levels
Jimenez.yepes et al. [14]	2008	Colombia (Medellin & Cali)	2004–2005	163	Female sex	Hospital records
Juvela et al. [33]	1993	Finland (Helsinki)	not given	278	HTN, Alcohol intake (recent), former and current smoking	In person interview with structured questionnaire
Kowalski & Nyquist [15]	2015	United States of America (Baltimore, Maryland)	1993–2009	933	Female sex, cold temperature	Hospital records
Koehy et al. [25]	2010	India (Kerala)	2003–2008	163	HTN, Smoking, Alcohol intake	Self-report
Kubota et al. [28]	2001	Japan	not given	127	Smoker, Drinker	Self-report
Ladenvall et al. [35]	2009	Sweden (Gothenburg)	2000–2004	183	FXIII haplotypes H2-H6, SNP Leu34 allele carriers	Genotyping
Morris et al. [27]	1992	England (Liverpool)	1990	144	Smoking	Hospital records
Okamoto et al. [19]	2001	Japan (Nagoya)	1992–1997	195	Age at menarche, Parity, Age at first pregnancy, Menopausal status, Menstrual cycle regularity, Age at first child birth, Parity, Gravidity	In person interview with structured questionnaire
Okamoto et al. [34]	2003	Japan (Nagoya)	1992–1997	201	Family history	In person interview with structured questionnaire
Okamoto et al. [26]	2005	Japan (Nagoya)	1992–1997	124	HTN, Smoking	In person interview with structured questionnaire
Olsson et al. [36]	2010	Sweden (Gothenburg)	2000–2004	183	Genetic variation on 9p21	Genotyping
Pettiti & Wingerd [22]a	1978	United States of America (California)	1969–1971	11	Current OCP use, Smoking, HTN, Migraine history	Self-report &/or PE
Ruiz-Sandoval et al. [16]	2009	Mexico	2002–2004	231	Female sex	Medical records & standardized questionnaire
Slowik et al. [17]	2004	Poland (Kraków)	2003–2004	90	b/b genotype of intron-4 27 bp VNTR polymorphism, Female sex	PCR & Hospital records
Staalso et al. [10]	2014	Denmark (Copenhagen)	2006–2011	333	Genotype II of the ACE gene, Female sex	Genotyping
Vlak et al. [39]	2013	Netherlands (Utrecht)	2006–2009	250	HTN, Smoking, Family history, High cholesterol	Medical records & questionnaire
You et al. [11]a	2010	South Korea (Seoul)	1995–2006	167	Female sex	Hospital records

Abbreviations: ACE: Angiotensin converting enzyme, ADAMTS13: A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif, 13, ALT: Alkaline aminotransferase, AST: Aspartate aminotransferase, CAD: Coronary artery disease, DM: Diabetes Mellitus, FXIII: Factor XIII, GpIIIa; Glycoprotein IIIa, HTN: Hypertension NOS3; Nitric oxide synthase gene, OCP: Oral contraceptive pill, PCR: Polymerase chain reaction, RFFLP: Restriction fragment length polymorphism, SNP: Single nucleotide polymorphism, VNTR: Variable number of tandem repeats.

a Nested case-control studies.

Table 3
Cohort studies: Risk factors in included studies.

Author	Year of publication	Country	Study years	Cases of aSAH (cases/person yr)	Risk factors	Assessment of risk factors
Lindekleiv et al. [20]	2011	Norway (Nord-Trøndelag County & Tromsø)	1994-1997	120 (14.6/100,000 person-years in women & 8.8100,000 person-years in men)	Age, HTN, SBP, Smoking, Alcohol, Family history, Age at menarche, Menopausal status, HT use, Parity	Self-report & physical examination
Lindegard et al. [23]	1987	Sweden (Gothenburg)	1970-1979	551	SAH predilection area & marital status	Medical records
Sandvei et al. [18]	2009	Norway (Nord-Trøndelag County & Tromsø)	1984-2005	132 (9.9/100,00 person-years)	Female sex	Physical examination, blood samples, self-report
Sandvei et al. [12]	2012	Norway (Nord-Trøndelag County & Tromsø)	1994-2007	122 (122/977895 person-years)	Female sex	Physical examination, blood samples, self-report

Abbreviations: HTN: Hypertension, HT: Hormone therapy, SBP: Systolic blood pressure.

menarche at age 12–13; menarche at < 12 years or > 13 years was not a risk factor for aSAH [20].

There was one case-control study on irregular menstrual cycle which showed that it was not a risk factor for aSAH [19].

Parity was reported as a risk factor for aSAH by two case-control studies and one cohort study. In one case-control study, authors reported that increasing parity moderately reduced the risk for aSAH [21]. The authors in this study categorized parity from primiparous to multiparous with ≥ 5 childbirths and found inverse association of risk with increasing parity. Similar findings were reported in another case-control study where nulliparity significantly increased the risk when parity ≥ 1 was taken as a reference [19]. In a cohort study, nulliparity and multiparous women with > 3 children were not associated with any association for aSAH when parity with 1–3 children was taken as a reference [20]. One case-control study observed that first child birth at ≥ 26 years was not associated with a risk for aSAH [19].

One case-control explored the risk of nulligravidity when being gravida with of ≥ 1 children was a reference and observed an increased risk for aSAH [19]. In the same case-control study, first pregnancy at age ≥ 26 years was a risk factor for aSAH [19].

Two studies mentioned oral contraceptive pills (OCPs) as a risk factor. One case-control examined current and past OCPs use as a risk factor for aSAH. An increased risk for aSAH was observed which was further accentuated in smokers [22]. One cohort study proposed that high dose OCPs could be a risk for aSAH in young women but did not further explore an association for aSAH [23]. One cohort study examined hormone replacement (HT)as a risk factor, it was reported that HT use is not associated with a risk of aSAH [20].

Two studies explored association of pre or post-menopausal women and aSAH. In one case-control did not find pre-menopause as a risk factor for aSAH when post-menopausal were taken as a reference [19]. While in cohort study, authors did not find post-menopause to increase the risk for aSAH when pre-menopausal women were a reference group [20].

One cohort study examined marital status and found that being divorced increased the risk for aSAH in women but not in spinsters, widowed and married women [23]. In the same study, authors reported that women living in aSAH predilection; which were the three districts in Gothenburg (Sweden) with most of the young population, with an increased number of divorcees and strikingly high number of cases of aSAH area, also increased the risk [23].

3.1.3. Smoking

3.1.3.1. Current smoking. All studies of the association between smoking and aSAH in men and women were of high quality (Appendix C Supplementary Table C.7, Appendix D Supplementary Fig. D.2 and D.3). One cohort study reported crude risks for men (RR 3.47) and women (RR 6.50) [20] and six case-control studies [24–29] provided crude estimates for comparing sex difference for smoking quantitatively in subgroup analysis. The OR_{crude} ranges in men (1.20–7.03) and women (1.93–5.70), and the $OR_{adjusted}$ ranges in men (1.1–6.08) and women (0.59–7.70) were similar. For pooled $OR_{adjusted}$, there were four case-control studies [26,30–32] for both sexes. Multivariable meta-analysis provided no evidence of sex difference for smoking (OR_{crude} $p = .984$ and $OR_{adjusted}$ $p = .95$).

Two case-control studies [30,33] provided risk of aSAH associated with current smoking stratified by dose. In both studies heavier smoking was associated with increased risk of aSAH in both sexes compared to low dose of smoking but more so in women than men.

3.1.3.2. Other smoking exposures. No sex difference in risk of aSAH associated with former smoking compared to non-smoking or current smoking was detected in multivariate meta-analysis between men and women ($p = .97$, Appendix B Supplementary Results, Appendix C Supplementary Table C.7, Appendix D Supplementary Fig. D.4).

Non-smokers exposed to environmental tobacco smoke (ETS) had a

different risk of aSAH to those not exposed in both sexes [30]. Ever smoking compared to never smoking was associated with a higher risk of aSAH in women but not men [25].

3.1.4. Alcohol consumption

Six studies (five case-control studies and one cohort study) provided evidence for an association between alcohol consumption and risk or odds of aSAH (OR_{crude} range: men 2.20–2.62; women 1.90–4.0, $OR_{adjusted}$ range: men 1.50–1.52; women, 0.80–0.95). See Appendix C Supplementary Table C.8, Appendix D Supplementary Fig. D.5 and D.6. In meta-analysis, two case-control studies [25,28] were included for pooled crude estimates and two case-control studies [31,32] for pooled adjusted estimates In multivariate meta-analysis, OR_{crude} was not different between sexes ($p = .94$), while for $OR_{adjusted}$ there was evidence for a stronger effect of alcohol consumption on men than women ($p = .003$). In one cohort study, authors did not report any association of alcohol consumption as a risk factor in both sexes [20].

One case-control study [33] categorized alcohol consumption within 24 h (1-40 g, 40–120 g, > 120 g), and within one week (1–150 g, 150–300 g, > 300 g) of the aSAH. Alcohol intake of 41-120 g within 24 h, and > 300 g was a risk for aSAH in both sexes but greater in women.

3.1.5. Blood pressure

Blood pressure was examined as a risk factor for aSAH in eight studies (seven case-control and one cohort) with measures including hypertension [20,22,24–26,31–33] and systolic blood pressure [20]. See Appendix C Supplementary Table C.9, Appendix D Supplementary Fig. D.7 and D.8.

In meta-analysis, four case-control studies [24–26,33] were included for pooled crude estimates and four case-control studies [25,26,31,32] for pooled adjusted estimates (OR_{crude} range: men 1.75–5.40; women 1.68–7.67, $OR_{adjusted}$ range: men 2.75–4.40; women 3.28–4.86). The results of multivariate meta-analysis provided no evidence of sex difference for hypertension (OR_{crude} $p = .82$, $OR_{adjusted}$ $p = .18$).

Increase in SBP was equally a risk for aSAH in both sexes in a cohort study (HR: men 1.23; women 1.16) [20].

3.1.6. Diabetes mellitus (DM)

Three case-control studies observed the association of DM and risk of aSAH in both sexes (OR_{crude} men 1.00; women 12.39, $OR_{adjusted}$ range: men 0.55–0.72; women 0.17–0.26). See Appendix C Supplementary Table C.10, Appendix D Supplementary Fig. D.9. The OR_{crude} was reported in one study [24]. For meta-analysis, two studies were included [31,32]. Diabetes mellitus was more protective in women than in men ($p = .01$) as evident from multivariate meta-analysis.

3.1.7. Coronary artery disease (CAD)

CAD was assessed a risk factor in two high-quality case-control studies ($OR_{adjusted}$ range: men 0.44–0.92; women 0.33–1.34). See Appendix C Supplementary Table C.11, Appendix D Supplementary Fig. D.10. Two studies were included for meta-analysis [31,32]. No risk for aSAH was detected in either sex. In multivariate meta-analysis, no sex difference was observed for the risk of aSAH was associated with CAD ($p = .87$).

3.1.8. Hypercholesterolemia and hypertriglyceridemia

There were three case-control studies examining hypercholesterolemia as a risk factor for aSAH in both sexes. See Appendix C Supplementary Table C.12, Appendix D Supplementary Fig. D.11. (OR_{crude} men 0.53; women 1.15, $OR_{adjusted}$ range: men 0.89–2.47; women 0.73–3.49). The included studies were of high quality. The OR_{crude} was reported in one study [24]. Two studies were included for meta-analysis [31,32] and no association was observed for the risk of

aSAH. In multivariate meta-analysis, there was no detectable sex difference for hypercholesterolemia as a risk for aSAH ($p = .88$) [24]. For hypertriglyceridemia, $OR_{crude\ in}$ men was 0.64 and in women was 1.00 (Appendix C Supplementary Table C.12) and was not found to be a risk factor in either sex in a case-control study [24].

3.1.9. Family history

Family history was analysed as a risk factor for aSAH in one case-control and one cohort study (Appendix C Supplementary Table C.13). In the case-control study, family history of aSAH was found to be an equally significant risk factor in both sexes. In the same study odds of aSAH associated with parental history of aSAH differed according to the sex of the parent. Positive maternal ($OR_{adjusted}$ 5.4, 95% CI; 1.8–16.0) and paternal history ($OR_{adjusted}$ 3.8, 95% CI; 1.1 to 13.4) were observed to be a risk factor, but only maternal history was significant in adjusted analysis [34]. In the cohort study, odds of aSAH was found to be twice as greater in women (HR_{crude} 2.16, 95% CI 1.36–3.44) than men (HR_{crude} 1.61, 95% CI 0.79–3.30 when there was a family history of stroke in univariable analysis [20].

3.1.10. Genetic risk factors

Six studies based on genetic variations or polymorphisms as a risk factor for aSAH were included (Appendix C Supplementary Table C.14). NOS3 27-bp-VNTR b/b genotype was associated with the risk of aSAH and was more prevalent in men [10] while clotting factor XIII gene variants increased risk of aSAH in women but not men [35]. Genetic variant rs10757278 on 9p21 also showed an association for the risk of aSAH in women [36]. Equal distribution of ACE gene genotype II was a risk factor for aSAH in both sexes [17]. Likewise, for ADAMST13 gene, no sex specific association was observed [37]. GpIIIa A1/A2 polymorphism neither was a risk factor in Polish population, nor was any sex difference detected [13].

3.1.11. Other risk factors

There were some other risk factors examined for their association with the risk of aSAH (Appendix C Supplementary Table C.15). Many important risk factors like age, low body mass index (BMI), use of drugs like cocaine and aspirin were mentioned in the several studies but could not be included because of the absence of sex specific analysis. In one study, stress was compared between the sexes by categorizing it into children related stress in women and work related stress in men but these were not significant risk factors for aSAH [38]. Increasing age was a risk factor in a cohort study in both sexes [20] and was associated with decreased risk of aSAH in age groups 35–45 years, 45–55 years and 55–65 years respectively with relative lifetime risk more in women compared to men [39]. In a study, authors reported cold temperature as a risk factor for aSAH in women but not men [15]. High alanine aminotransferase (ALT) levels were associated with risk of aSAH in men but not in women [31]. High aspartate aminotransferase (AST) levels were associated with reduced risk in men while no association with risk was reported in women [31]. Liver disease and urea nitrogen had no association for the risk of aSAH in either sex [31].

3.2. Analysis of heterogeneity by regions

We conducted meta-regression for the risk factors when there were 3 or more studies for a risk factor and a region was common for at least 2 studies. The region with high incidence was taken as reference. We could only analyse the difference by region for female sex (adjusted Odds ratio from case-control studies), smoking (adjusted and unadjusted Odds ratio), and hypertension (unadjusted Odds ratio). Regional differences in these risk factors were not statistically significant. See Appendix C Tables C.17–C.23.

6

4. Discussion

In this systematic review, risk factors for their sex-specific association with aSAH, were identified. Most risk factors had an equal effect on the risk or odds of aSAH in men and women. A large proportion of studies had to be excluded because there was no sex specific analysis of risk factors.

Female sex was associated with a greater risk of aSAH compared to male sex. This aligns with the findings of several female-only risk factors that are broadly related to greater exposure to reproductive hormones including early age at menarche, later age at pregnancy and nulligravidity. Women suffer from aSAH after menopause which suggests that estrogen might be important in protection against the rupture of aneurysm [40] though it might not be the main factor for aSAH [41]. Estrogen promotes vessel wall strengthening by increasing connective tissue and endothelial NO production, and decreasing TNF-α function which is pro-inflammatory cytokine [42]. The estrogenic change in menopausal women might stimulate aneurysm formation and rupture. The absence of this strong estrogen withdrawal in males could be one factor contributing to the lower incidence in men compared to women. The underlying explanation for this may be the number of menstrual cycles, which is greater in women with early age of menstruation [40]. Estrogen levels change markedly during the menstrual cycle, with a deficiency of estrogen in immediate perimenstrual phase. Estrogen deficiency can lead to changes in vascular hemodynamics and micro-anatomy increasing its fragility [43], as it is protective against vessel injury by producing nitric oxide which reduces oxidative stress [44] and, decreasing TNF-α function which is pro-inflammatory cytokine [42]. Therefore, the greater number of menstrual cycles in women, the greater the exposure to these estrogenic changes. There is a need for greater understanding of the role of hormones in cerebral aneurysm rupture as this may be a therapeutic target to reduce aSAH, particularly in women. This is unlikely to be a simple task given the conflicting effects of currently available therapies on risk of aSAH with oral contraceptives increasing [45] and hormone replacement therapy decreasing [46] the risk.

Risk factors such as smoking, hypertension, increased systolic blood pressure, family history of aSAH and age were associated with a similar increased risk of aSAH in both sexes. Although smoking was equally a risk factor for aSAH in both sexes there was some evidence of a larger risk of aSAH in women, compared to men, who smoked heavily [42]. Cigarette smoking can cause endothelial dysfunction, hemodynamic stress, and promote inflammatory response that affects extracellular matrix leading to the formation of aneurysm and, further breakdown of matrix and cell death causes to aneurysmal rupture [47]. Hypertension increases the risk of aSAH in men and women equally through damaging the endothelium, occluding vessel wall and connective tissue synthesis [42], and affecting the release of mediators like matrix metalloproteinase 13 [48] and nitric oxide (NO) [49]. Matrix metalloproteinase 13 breaks down extracellular matrix [48] and nitric oxide (NO) promotes oxidative stress [49], which can cause aneurysm rupture [42]. The role of family history in the occurrence of aSAH in men and women may be due to shared behavioural and genetic factors. Several genetic risk factors equally affected men and women including variation in ADAMTS13 gene [37] and ACE enzyme gene insertion/deletion polymorphism [17]. When endothelial injury occurs, ADAMTS13 protease inhibits thrombus formation and decreases vascular inflammation in response to contents released by platelets [50]. Therefore, variation in ADAMST13 gene is a possible pathophysiological mechanism for aSAH in men and women. Some authors observed that the insertion/deletion (I/D) polymorphism of the (ACE) gene increased the risk of aSAH [17]. This polymorphism is linked with hypertension [51], a known risk factor for aSAH, and with other cardiovascular diseases such as coronary artery disease [52] and ischemic stroke [53]. These finding suggest that the management of traditional risk factors for stroke through lifestyle modification and medications should remain the key

targets for primary prevention of aSAH, as well as stroke in general [54].

Some risk factors for aSAH were only present in men. This may be attributable to the dose of the risk factor. For example, the observation that alcohol consumption was more hazardous in men than women may be attributable to the heavier consumption of alcohol in men [25,28,33]. There are several mechanisms linking alcohol consumption to aSAH. High levels of alcohol consumption induce oxidative stress that damages the endothelium which may cause aneurysm formation and rupture [49]. Heavy alcohol consumption can lead to increase in blood pressure [55], which itself is an independent risk factor for aSAH. [56] In a related finding, higher ALT levels increased the risk of aSAH in men but not women. High ALT levels are usually associated with liver disease or cirrhosis of liver, alcoholism being one of the causes, making a plausible link to aSAH [57]. The mechanisms underlying the greater risk of aSAH in men than women associated with high ALT levels remain unknown [31]. Current primary prevention guidelines for stroke, which include aSAH, counsel against heavy alcohol consumption. This should be a focus of management for men with existing aneurysms [54]. Endothelial NOS gene (NOS3) 27-bp-VNTR b/b genotype polymorphism was also a risk for aSAH in men only [10]. It is unclear why men and not women with this polymorphism may have a greater risk of aSAH. However, as endothelial nitric oxide synthase (NOS) derives NO and is involved in vasodilation and protection from thrombosis, a pathophysiological link to aSAH is reasonable [58]. Increasingly knowledge of genetic risk factors for aneurysm rupture made lead to more individualised approaches to management of people with aneurysms.

Some risk factors were associated with an increased risk of aSAH in women but not in men. Clotting factor XIII gene haplotypes H2 & H3 were associated with the risk of aSAH in women but not men. In the same study, Ladenvall et al. reported carriers of FXIII 34Leu allele were also associated with the risk of aSAH more in women than in men [35]. Coagulation factor XIII induces cross-linking of fibrin for strengthening the thrombus and wound healing [59]. The variation in 9p21 (lead SNPrs10757278) was also a risk factor for aSAH in women. The association between 9p21 and cerebral aneurysm, aortic aneurysms, coronary artery disease, and ischaemic stroke has been observed in previous studies [60–62]. The authors of these studies did not explore why these particular factors may increase risk in women but not men. We hypothesize that statistical power may have contributed as these studies tended to include more women (74%) than men. In some studies, there were trends towards an association in men, but these failed to reach significance. Larger samples, potentially through individual participant data analyses, may be required to examine these sex differences in detail. The differences in genetic variations could potentially explain the sex differences in aSAH. With replication of these findings in larger datasets, genetic risks for aSAH hold promise as tools to identify people with aneurysms at high risk of rupture that should undergo securement.

Some risk factors had inverse association with the risk or odds of aSAH in men and women. High levels of AST were associated with a reduced risk of aSAH in men for reasons that are not clear [31]. Diabetes mellitus decreased the risk of aSAH in women but not men, although a similar non-significant trend was noted in men. Others have suggested that people with diabetes might have a greater risk of dying from other causes and thus the chances of SAH occurrence is less [6]. Diabetics have higher BMI which is associated with a lower risk of aSAH [12] for reasons that are not clear. Diabetics may change their lifestyles through healthier diets and be more likely to take medications for hypertension [63] which might prevent the rupture of the aneurysm. There were some factors that were not found to be associated with risk of aSAH in either sex, including former smoking, coronary artery disease, hypercholesterolemia, hypertriglyceridemia, liver disease and urea nitrogen.

There were several limitations of our study. Firstly, only published data was used, and therefore, some studies that were unpublished because of negative findings may have been missed. Secondly, many

important risk factors were not addressed separately in men and women such as life style factors (e.g. BMI, physical activity), environmental factors (e.g. seasonal fluctuations, pollution), ethnicity, and anatomical location and morphology of aneurysm. Most studies based on risk factors, did not aim to find sex differences in risk factors for aSAH. There were very few studies for each risk factor; therefore, pooled estimates might be underpowered to explore the sources of heterogeneity. All studies showed that aneurysm presence was confirmed through angiographic techniques or during surgery or at autopsy, but we included the studies which mentioned presence of aneurysm in all cases but not the means of how it was confirmed, which was another limitation. The strengths of the study are use of the comprehensive list of risk factors in our search strategy, systematic approach, wide time-period, and inclusion of studies with genetic risk factors.

In conclusion, it was surprising that not many risk factors for aSAH differed between the sexes given the difference in incidence between men and women. Many studies identified could not be included as the data were not reported separately for men and women. There should be efforts to undertake secondary analyses of these existing studies. This will help us to understanding the risk factors for aSAH in men and women and inform prevention efforts. It should be noted that the prevalence of unruptured intracranial aneurysms (UIA) is greater in women than in men with prevalence ratio of 1.61(1.02–2.54) [64] and earlier identification could alleviate the burden of aSAH incidence in women. The clinical guidelines for UIA do not mention women as a high-risk group [65]; a point to ponder over. We also recommend studies exploring aSAH risk factors linked to hormones, as these may assist prevention and management of aneurysmal rupture in women but also men. In the meantime, the management of known risk factors for aSAH including hypertension, smoking and heavy alcohol consumption, should be the focus of efforts to prevent aSAH in men and women.

Contribution

SG designed the study.SG and SR built a search strategy. SR and BS reviewed the articles for title and abstract and full text and, any conflicts between the reviewers were resolved by SG. SR and MD did data extraction and quality assessments and SG resolved any conflicts between the reviewers. MB, PO planned analysis and SR did the analysis. MB, PO and HP did data interpretation. SR wrote the article with assistance from SG, MC, MB, PO, AGT, HP and RVC. All authors reviewed the article before its submission.

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Declaration of Competing Interest

We declare no conflict of interests.

Appendix A. Supplementary data

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References

[1] L. Nichols, C. Stirling, P. Otahal, J. Stankovich, S. Gall, Socioeconomic disadvantage is associated with a higher incidence of aneurysmal subarachnoid hemorrhage, J. Stroke Cerebrovasc. Dis.: Off. J. Natl. Stroke Assoc. 27 (3) (2018) 660–668.
[2] H. Lindekleiv, I. Njølstad, T. Ingebrigtsen, E. Mathiesen, Incidence of aneurysmal subarachnoid hemorrhage in Norway, 1999–2007, Acta Neurol. Scand. 123 (1) (2011) 34–40.
[3] J. van Gijn, R.S. Kerr, G.J.E. Rinkel, Subarachnoid haemorrhage, Lancet 369 (9558) (2007) 306–318.
[4] K. Harada, K. Fukuyama, T. Shirouzu, M. Ichinose, H. Fujimura, K. Kakumoto, et al., Prevalence of unruptured intracranial aneurysms in healthy asymptomatic Japanese adults: differences in gender and age, Acta Neurochir. 155 (11) (2013) 2037–2043.
[5] L.L. Teunissen, G.J. Rinkel, A. Algra, J. van Gijn, Risk factors for subarachnoid hemorrhage: a systematic review, Stroke 27 (3) (1996) 544–549.
[6] V.L. Feigin, G.J. Rinkel, C.M. Lawes, A. Algra, D.A. Bennett, J. van Gijn, et al., Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies, Stroke 36 (12) (2005) 2773–2780.
[7] G.A.S.B. Wells, D. O'Connell, et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[8] I.R. White, Multivariate random-effects meta-analysis, Stata J. 9 (1) (2009) 40–56.
[9] A. Can, V.M. Castro, Y.H. Ozdemir, S. Dagen, S. Yu, D. Dligach, et al., Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation, Neurology. 89 (13) (2017) 1408–1415.
[10] J.M. Staalso, T. Edsen, A. Kotinis, B. Romner, J.B. Springborg, N.V. Olsen, Association of the NOS3 intron-4 VNTR polymorphism with aneurysmal subarachnoid hemorrhage, J. Neurosurg. 121 (3) (2014) 587–592.
[11] S.-H. You, D.-S. Kong, J.-S. Kim, P. Jeon, K.H. Kim, H.K. Roh, et al., Characteristic features of unruptured intracranial aneurysms: predictive risk factors for aneurysm rupture, J. Neurol. Neurosurg. Psychiatry 81 (5) (2010) 479–484.
[12] M.S. Sandvei, H. Lindekleiv, P.R. Romundstad, T.B. Müller, L.J. Vatten, T. Ingebrigtsen, et al., Risk factors for aneurysmal subarachnoid hemorrhage - BMI and serum lipids: 11-year follow-up of the HUNT and the tromso study in Norway, Acta Neurol. Scand. 125 (6) (2012) 382–388.
[13] M.G. Adamski, A. Borratynska, M. Krupa, D. Wloch-Kopec, W. Turaj, P. Wolkow, et al., A1/A2 polymorphism of GPIIIA gene and a risk of aneurysmal subarachnoid haemorrhage, Biochem. Biophys. Res. Commun. 383 (2) (2009) 228–230.
[14] C.M. Jimenez-Yepes, J.L. Londono-Fernandez, Risk of aneurysmal subarachnoid hemorrhage: the role of confirmed hypertension, Stroke. 39 (4) (2008) 1344–1346.
[15] R. Kowalski, N.P. 472, Role of temperature and humidity in aneurysmal subarachnoid hemorrhage onset a comparative analysis, Crit. Care Med. 43 (12) (2015) 119–120.
[16] J.L. Ruiz-Sandoval, C. Cantu, E. Chiquete, C. Leon-Jimenez, A. Arauz, L.M. Murillo-Bonilla, et al., Aneurysmal subarachnoid hemorrhage in a Mexican multicenter registry of cerebrovascular disease: the RENAMEVASC study, J. Stroke Cerebrovasc. Dis. 18 (1) (2009) 48–55.
[17] A. Slowik, A. Borratynska, J. Pera, M. Betlej, T. Dziedzic, T. Krzyszkowski, et al., II genotype of the angiotensin-converting enzyme gene increases the risk for subarachnoid hemorrhage from ruptured aneurysm, Stroke. 35 (7) (2004) 1594–1597.
[18] M.S. Sandvei, P.R. Romundstad, T.B. Müller, L. Vatten, A. Vik, Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway, Stroke 40 (6) (2009) 1958–1962.
[19] K. Okamoto, R. Horisawa, T. Kawamura, A. Asai, M. Ogino, T. Takagi, et al., Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: a case-control study in Nagoya, Japan, Stroke 32 (12) (2001) 2841–2844.
[20] H. Lindekleiv, M.S. Sandvei, I. Njolstad, M.L. Lochen, P.R. Romundstad, L. Vatten, et al., Sex differences in risk factors for aneurysmal subarachnoid hemorrhage: a cohort study, Neurology. 76 (7) (2011) 637–643.
[21] D. Gaist, L. Pedersen, S. Cnattingius, H.T. Sorensen, Parity and risk of subarachnoid hemorrhage in women: a nested case-control study based on national Swedish registries, Stroke. 35 (1) (2004) 28–32.
[22] D.B. Petitti, J. Wingerd, Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage, Lancet. 2 (8083) (1978) 234–235.
[23] B. Lindegård, M. Hillbom, S. Brody, High-dose estrogen-progestagen oral contraceptives: a risk factor for aneurysmal subarachnoid hemorrhage? Acta Neurol.

Scand. 76 (1) (1987) 37–45.

[24] P. Canhao, A.N. Pinto, H. Ferro, J.M. Ferro, Smoking and aneurysmal subarachnoid haemorrhage: a case-control study, J. Cardiovasc. Risk 1 (2) (1994) 155–158.

[25] L. Koshy, H.V. Easwer, S. Premkumar, J.P. Alapatt, A.M. Pillai, S. Nair, et al., Risk factors for aneurysmal subarachnoid hemorrhage in an Indian population, Cerebrovasc. Dis. (Basel, Switzerland). 29 (3) (2010) 268–274.

[26] K. Okamoto, R. Horisawa, Y. Ohno, The relationships of gender, cigarette smoking, and hypertension with the risk of aneurysmal subarachnoid hemorrhage: a case-control study in Nagoya, Japan, Ann. Epidemiol. 15 (10) (2005) 744–748.

[27] K.M. Morris, M.D. Shaw, P.M. Foy, Smoking and subarachnoid haemorrhage: a case control study, Br. J. Neurosurg. 6 (5) (1992) 429–432.

[28] M. Kubota, A. Yamaura, J. Ono, Prevalence of risk factors for aneurysmal subarachnoid haemorrhage: results of a Japanese multicentre case control study for stroke, Br. J. Neurosurg. 15 (6) (2001) 474–478.

[29] B.A. Bell, L. Symon, Smoking and subarachnoid haemorrhage, Br. Med. J. 1 (6163) (1979) 577–578.

[30] C.S. Anderson, V. Feigin, D. Bennett, R.B. Lin, G. Hankey, K. Jamrozik, Active and passive smoking and the risk of subarachnoid hemorrhage: an international population-based case-control study, Stroke 35 (3) (2004) 633–637.

[31] T. Inagawa, Risk factors for aneurysmal subarachnoid hemorrhage in patients in Izumo City, Japan, J. Neurosurg. 102 (1) (2005) 60–67.

[32] T. Inagawa, Risk factors for the formation and rupture of intracranial saccular aneurysms in Shimane, Jpn. World Neurosurg. 73 (3) (2010) 155–164 (discussion e23).

[33] S. Juvela, M. Hillbom, H. Numminen, P. Koskinen, Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage, Stroke 24 (5) (1993) 639–646.

[34] K. Okamoto, R. Horisawa, T. Kawamura, A. Asai, M. Ogino, T. Takagi, et al., Family history and risk of subarachnoid hemorrhage: a case-control study in Nagoya, Japan, Stroke 34 (2) (2003) 422–426.

[35] C. Ladenvall, L. Csajbok, K. Nylen, K. Jood, B. Nellgard, C. Jern, Association between factor XIII single nucleotide polymorphisms and aneurysmal subarachnoid hemorrhage, J. Neurosurg. 110 (3) (2009) 475–481.

[36] S. Olsson, L.Z. Csajbok, K. Jood, K. Nylen, B. Nellgard, C. Jern, Association between genetic variation on chromosome 9p21 and aneurysmal subarachnoid haemorrhage, J. Neurol. Neurosurg. Psychiatry 82 (4) (2011) 384–388.

[37] E. Hanson, S. Olsson, B. Bayazit, L.Z. Csajbok, K. Nylen, B. Nellgard, et al., Association between variation in ADAMTS13 and aneurysmal subarachnoid hemorrhage, Thromb. Res. 131 (1) (2013) 99–101.

[38] A.G. de Wilde P., G.J.E. Rinkel, A. Algra, Stress and aneurysmal subarachnoid haemorrhage: case control study, Cerebrovasc. Dis. (Basel, Switzerland) 35 (Suppl. 3) (2013) 55.

[39] M.H. Vlak, G.J. Rinkel, P. Greebe, J.P. Greving, A. Algra, Lifetime risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification, J. Neurol. Neurosurg. Psychiatry 84 (6) (2013) 619–623.

[40] S. Tabuchi, Relationship between postmenopausal estrogen deficiency and aneurysmal subarachnoid hemorrhage, Behav. Neurol. 2015 (2015).

[41] Y.X. Wang, J. He, L. Zhang, Y. Li, L. Zhao, H. Liu, et al., A higher aneurysmal subarachnoid hemorrhage incidence in women prior to menopause: a retrospective analysis of 4,895 cases from eight hospitals in China, Quant. Imaging in Med. Surg. 6 (2) (2016) 151–156.

[42] T.H. Andreasen, J. Bartek, M. Andresen, J.B. Springborg, B. Romner, Modifiable risk factors for aneurysmal subarachnoid hemorrhage, Stroke 44 (12) (2013) 3607–3612.

[43] H. Handa, N. Hashimoto, I. Nagata, F. Hazama, Saccular cerebral aneurysms in rats: a newly developed animal model of the disease, Stroke. 14 (6) (1983) 857–866.

[44] Y. Tada, H. Makino, H. Furukawa, K. Shimada, K. Wada, E.I. Liang, et al., Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice, Neurosurgery. 75 (6) (2014) 690–695.

[45] S.C. Johnston, J.M. Colford Jr., D.R. Gress, Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis, Neurology 51 (2) (1998) 411–418.

[46] C.N. Mhurchu, C. Anderson, K. Jamrozik, G. Hankey, D. Dunbabin, Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: an international population-based, case-control study, Stroke 32 (3) (2001) 606–612.

[47] N. Chalouhi, M.S. Ali, R.M. Starke, P.M. Jabbour, S.I. Tjoumakaris, L.F. Gonzalez, et al., Cigarette smoke and inflammation: role in cerebral aneurysm formation and rupture, Mediat. Inflamm. 2012 (2012).

[48] M.F. Leeman, S. Curran, G.I. Murray, The structure, regulation, and function of human matrix metalloproteinase-13, Crit. Rev. Biochem. Mol. Biol. 37 (3) (2002) 149–166.

[49] R.M. Starke, N. Chalouhi, M.S. Ali, P.M. Jabbour, S.I. Tjoumakaris, L.F. Gonzalez, et al., The role of oxidative stress in cerebral aneurysm formation and rupture, Curr. Neurovasc. Res. 10 (3) (2013) 247–255.

[50] X.L. Zheng, ADAMTS13 and von Willebrand factor in thrombotic thrombocytopenic purpura, Annu. Rev. Med. 66 (2015) 211–225.

[51] R. Krishnan, D. Sekar, S. Subramanium, Association of angiotensin converting enzyme gene insertion/deletion polymorphism with essential hypertension in south Indian population, Genes Dis. 3 (2) (2016) 159–163.

[52] S. Dhar, S. Ray, A. Dutta, B. Sengupta, S. Chakrabarti, Polymorphism of ACE gene as the genetic predisposition of coronary artery disease in Eastern India, Indian Heart J. 64 (6) (2012) 576–581.

[53] Z. Zhang, G. Xu, D. Liu, X. Fan, W. Zhu, X. Liu, Angiotensin-converting enzyme insertion/deletion polymorphism contributes to ischemic stroke risk: a meta-analysis of 50 case-control studies, PLoS One 7 (10) (2012) e46495.

[54] E.S. Connolly Jr., A.A. Rabinstein, J.R. Carhuapoma, C.P. Derdeyn, J. Dion, R.T. Higashida, et al., Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 43 (6) (2012) 1711–1737.

[55] N.M.T. Santana, J.G. Mill, G. Velasquez-Melendez, A.D. Moreira, S.M. Barreto, M.C. Viana, et al., Consumption of alcohol and blood pressure: results of the ELSA-Brasil study, PLoS One 13 (1) (2018) e0190239.

[56] H. Ohkuma, H. Tabata, S. Suzuki, M.S. Islam, Risk factors for aneurysmal subarachnoid hemorrhage in Aomori, Japan, Stroke. 34 (1) (2003) 96–100.

[57] N.S. Parikh, A.E. Merkler, A. Jesudian, H. Kamel, Association between cirrhosis and aneurysmal subarachnoid hemorrhage, Ann. Clin Transl. Neurol. 6 (1) (2019) 27–32.

[58] D. Tousoulis, A.M. Kampoli, C. Tentolouris, N. Papageorgiou, C. Stefanadis, The role of nitric oxide on endothelial function, Curr. Vasc. Pharmacol. 10 (1) (2012) 4–18.

[59] R.A. Ariëns, T.-S. Lai, J.W. Weisel, C.S. Greenberg, P.J. Grant, Role of factor XIII in fibrin clot formation and effects of genetic polymorphisms, Blood. 100 (3) (2002) 743–754.

[60] A. Helgadottir, G. Thorleifsson, K.P. Magnusson, S. Grétarsdottir, V. Steinthorsdottir, A. Manolescu, et al., The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm, Nat. Genet. 40 (2) (2008) 217.

[61] N.J. Samani, J. Erdmann, A.S. Hall, C. Hengstenberg, M. Mangino, B. Mayer, et al., Genomewide association analysis of coronary artery disease, N. Engl. J. Med. 357 (5) (2007) 443–453.

[62] M. Matarin, W.M. Brown, A. Singleton, J.A. Hardy, J.F. Meschia, Whole genome analyses suggest ischemic stroke and heart disease share an association with polymorphisms on chromosome 9p21, Stroke 39 (5) (2008) 1586–1589.

[63] X.-Y. Yao, C.-Q. Jiang, G.-L. Jia, G. Chen, Diabetes mellitus and the risk of aneurysmal subarachnoid haemorrhage: a systematic review and meta-analysis of current evidence, J. Int. Med. Res. 44 (6) (2016) 1141–1155.

[64] M.H. Vlak, A. Algra, R. Brandenburg, G.J. Rinkel, Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis, Lancet Neurol. 10 (7) (2011) 626–636.

[65] B.G. Thompson, R.D. Brown Jr., S. Amin-Hanjani, J.P. Broderick, K.M. Cockroft, E.S. Connolly Jr.et al., Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 46 (8) (2015) 2368–2400.

9

Appendix D: Publication 2

ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Sex differences in aneurysmal subarachnoid haemorrhage (aSAH): aneurysm characteristics, neurological complications, and outcome

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Abstract

Background Women are over-represented in aSAH cohorts, but whether their outcomes differ to men remains unclear. We examined if sex differences in neurological complications and aneurysm characteristics contributed to aSAH outcomes.

Methods In a retrospective cohort (2010–2016) of all aSAH cases across two hospital networks in Australia, information on severity, aneurysm characteristics and neurological complications (rebleed before/after treatment, postoperative stroke < 48 h, neurological infections, hydrocephalus, seizures, delayed cerebral ischemia [DCI], cerebral infarction) were extracted. We estimated sex differences in (1) complications and aneurysm characteristics using chi square/t-tests and (2) outcome at discharge (home, rehabilitation or death) using multinomial regression with and without propensity score matching on prestroke confounders.

Results Among 577 cases (69% women, 84% treated) aneurysm size was greater in men than women and DCI more common in women than men. In unadjusted log multinomial regression, women had marginally greater discharge to rehabilitation (RRR 1.15 95% CI 0.90–1.48) and similar likelihood of in-hospital death (RRR 1.02 95% CI 0.76–1.36) versus discharge home. Prestroke confounders (age, hypertension, smoking status) explained greater risk of death in women (rehabilitation RRR 1.13 95% CI 0.87–1.48; death RRR 0.75 95% CI 0.51–1.10). Neurological complications (DCI and hydrocephalus) were covariates explaining some of the greater risk for poor outcomes in women (rehabilitation RRR 0.87 95% CI 0.69–1.11; death RRR 0.80 95% CI 0.52–1.23). Results were consistent in propensity score matched models.

Conclusion The marginally poorer outcome in women at discharge was partially attributable to prestroke confounders and complications. Improvements in managing complications could improve outcomes.

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Introduction

In contrast to other stroke types, women have a greater incidence of aneurysmal subarachnoid haemorrhage (aSAH) than men [29, 43]. In some studies, female sex has been shown to be an independent determinant of poor outcome following aSAH, with greater 30-day case-fatality [30] and poorer 2-year outcome [8, 32, 35, 42] than men. Others have reported that sex is not a prognostic factor for outcome following aSAH [12, 20, 25, 34]. Few studies have been specifically designed to examine sex differences in outcome after aSAH. In our previous research including mostly ischaemic strokes, we determined that characteristics before stroke such as age and comorbidities, but also more modifiable factors such as stroke severity and aspects of clinical management were contributing to poorer outcomes for women compared with men [16, 31]. There has been limited research exploring patient-level factors that may explain sex differences in outcome after aSAH. Such findings are potentially important clinically because they may lead to sex-specific interventions to improve management and outcome.

Aneurysm characteristics and neurological complications predict outcome after aSAH [20, 32, 34]. There is also some evidence that these vary by sex, suggesting that these could mediate any sex differences in outcome after aSAH. Delayed cerebral ischemia (DCI) occurs in nearly 30% of patients [36] and is the most important cause of mortality and morbidity for aSAH. While some authors have reported that the incidence of DCI was greater in women than men [11, 17], authors of a systematic review concluded that there was limited evidence of a sex difference, but that only one out of four studies was of high quality [33]. Among other neurological complications, hydrocephalus has been reported to be more frequent in women than men [38], rebleeding more common in men than women [7], while no detectable sex difference has been reported for seizures [5]. Aneurysm characteristics including location (e.g. posterior circulation) [20] and larger size [8, 20, 34] are associated with poor outcome. Some researchers have reported sex differences in site and location of ruptured aneurysm [12, 18, 20]. Most of these studies were not designed to examine sex differences in complications, had small sample sizes and few used standardised assessment of complications. No studies though have explored how differences in aneurysm characteristics between men and women may influence outcome.

We therefore aimed to examine sex differences in (1) neurological complications, (2) aneurysm characteristics, (3) discharge outcomes including the role of complications and aneurysm characteristics in any differences observed. We hypothesised that compared with men, women would more often have unfavourable aneurysm characteristics and complications that would result in worse outcomes after aSAH.

Methods

This was a retrospective cohort study of all patients with aSAH across two tertiary referral hospital networks (Tasmania, population ~ 500,000 and South East Victoria, population ~ 1.2 million) in Australia from 1st January 2010 to 31st December 2016. Both hospitals are comprehensive cerebrovascular centres, receiving patients who experience aSAH from a network of urban, regional and rural hospitals. This study was approved by the Human Research Ethics Committee in Victoria (RES-18-0000-036A) and Tasmania (H0014563). Potential cases were identified using multiple overlapping sources including admission, discharge and ward lists for emergency, neurosurgical and radiology departments across the tertiary centres and referring hospitals. A combination of International Classification of Diseases 10 codes (I60.0–I60.9, I67.1 and I69.0), as either a primary or secondary diagnosis, and keyword searches were used to ascertain potential cases. A standardised extraction form using data from radiology, pathology and surgical reports, as well as the medical record were used to confirm first ever aSAH. Potential cases were coded by one researcher in each site, and a neurosurgeon and/or an interventional neuroradiologist confirmed the diagnoses and resolved any discrepancies. Following detailed review of medical records, patients with unruptured aneurysms were excluded, and only those with confirmed SAH included in the final sample.

The presence of subarachnoid haemorrhage was confirmed on either non-contrast CT-brain or xanthochromia on lumbar puncture. CT-angiography, digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) was then used to find a cause, including an aneurysm, and characterise it. We excluded cases with previous history of aSAH and other causes of subarachnoid haemorrhage including arteriovenous malformations (AVMs), trauma, amyloid angiopathy and nonaneurysmal SAH. The latter were only excluded where, despite multiple series of imaging tests, a cerebral aneurysm could not be demonstrated. After verifying the aneurysmal cause of SAH, information was extracted from the medical record and captured in REDCap [21].

Covariates

Aneurysm characteristics

We extracted information for side of aneurysm, anterior or posterior part of circulation, site on Circle of Willis and maximal size in millimetres. The information was collected from neuroradiological reports from neuroimaging (e.g. CT scans and DSAs). The location of the aneurysm was categorised into

five groups, including posterior communicating artery, internal carotid artery (anterior choroidal and internal carotid excluding posterior communicating), anterior cerebral artery (A1 precommunicating part of anterior cerebral artery which originates from the terminal bifurcation of the internal carotid artery, extending almost 14 mm in length, terminating at the anterior communicating and pericallosal artery), middle cerebral artery (M1 which is the horizontal segment of middle cerebral artery, at bifurcation and, distal middle cerebral artery) and posterior circulation (posterior cerebral branches, basilar, vertebral, superior cerebellar, anterior inferior cerebellar, posterior inferior cerebellar, vertebrobasilar junction). We categorized aneurysm size into four groups based on previous literature, ≤ 6.9 mm, 7–9.9 mm, 10–19.9 mm and ≥ 20 mm [4]. In a small number of patients, the size of aneurysm could not be determined due to absence of information in the respective records, and so these were categorised as missing.

Complications

Neurological complications were abstracted based on the National Institute of Neurological Disorders and Stroke definitions (NINDS) [40]. These included postoperative stroke within 48 h, posttreatment neurological infections, rebleed, hydrocephalus (defined by the presence of an intervention), seizures, DCI (based on clinical criteria) and cerebral infarction (based on radiological evidence). Treatments for complications were also extracted. These included ventriculostomy/ external ventricular drain (EVD) or shunt placement for pre- and postoperative hydrocephalus, and endovascular balloon angioplasty or intraarterial vasodilators for DCI.

Outcome

Outcome was categorized according to the discharge destination after acute admission which included discharge to home, discharge to rehabilitation or in-hospital death.

Patient characteristics

Patient characteristics, prestroke clinical and behavioural factors' details were extracted from medical records including age, smoking status (current smoker, ex-smoker and non-smoker), history of high blood pressure (antihypertensive medications on admission and/or recorded history), World Federation of Neurological Surgeons severity grading (WFNS from neurosurgical or neuroradiological records) and modified Fisher scores (higher score depicted worse prognosis from neurosurgical or neuroradiological records), medications (antihypertensive agents and nimodipine), type of treatment for aneurysm (coiling or clipping) and hospital network.

Statistical analysis

We examined sex differences in the aneurysm characteristics and neurological complications using Pearson's chi square for categorical variables and t test for continuous variables.

We used log multinomial regression to estimate the relative risk ratio (RRR ± 95% confidence interval [CI]) of discharge to rehabilitation or death in-hospital compared with discharged home for women compared with men. We built two multivariable models: the first to estimate the effect of sex on outcome independent of 'pre-stroke confounding factors' such as demographic and clinical factors (model 1), and the second to include 'covariates' which include aneurysm characteristics and complications to examine their additional effect (model 2). We identified potential prestroke confounding factors to include in our models that were known to be associated with poor outcome from existing literature as well as analyses of study factors (e.g. demographics, pre-stroke health or clinical factors). We examined variables for confounder adjusted model if they were different by sex in our study. We used purposeful model building to create a model adjusted for prestroke confounders selecting to include a variable in the model when (1) the covariate was associated with sex (p value ≤ 0.25), (2) the covariate was associated with the outcome (p value ≤ 0.25) and (3) the covariate that changed the effect of sex on the outcome by ≥ 10% [19, 31]. As our objective was to examine whether aneurysm characteristics or complications contributed to sex differences in discharge destination, we entered aneurysm characteristics and complications that were different by sex as covariates into the confounder adjusted model. Changes in the magnitude of effect for sex on the outcome when adjusted for aneurysm characteristics or complications would suggest these factors contribute to sex differences in outcome. We explored interactions between sex and covariates using product terms in the final multivariable models.

We performed sensitivity analyses using propensity score matching as an alternative to the classical confounder adjusted models. We created propensity scores to match men and women based on prestroke confounders different by sex, and then applied weights based on the propensity score to the multinomial logistic regression. Aneurysm characteristics and complications that differed by sex were entered into the weighted model as covariates. Analysis was performed in statistical software Stata15 (StataCorp LLC, Texas, USA) and a two-sided p value < 0.05 was considered statistically significant.

Results

There were 577 confirmed cases of aSAH. Women were over-represented (69% of cases; Table 1). Data were generally complete with < 1% missing details of discharge destination and < 10% missing details of aneurysm characteristics or complications.

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Table 1 Characteristics of cohort

Variable	Men[§] N = 179 N	(%)	Women[§] N = 398 N	(%)	P value
No of patients (%)	179	(31)	398	(69)	
Mean age (SD)	54.44 (14.94)		57.78 (15.34)		0.01*
Age category					0.18
≤55 years	94	(53)	185	(46)	
>55 years	85	(47)	213	(54)	
Smoking					0.10
Current smoker	92	(51)	171	(43)	
Ex-smoker	25	(14)	36	(9)	
Non-smoker	32	(18)	90	(23)	
Missing	30	(17)	101	(25)	
Hypertension					0.006**
Yes	61	(34)	187	(47)	
No	110	(61)	200	(50)	
Missing	8	(4)	11	(3)	
Charlson comorbidity index					0.23
0 or 1	157	(88)	334	(84)	
≥2	22	(12)	64	(16)	
States					0.48
Victoria	106	(59)	248	(62)	
Tasmania	73	(41)	150	(38)	
WFNS					0.37
I	88	(49)	166	(42)	
II	28	(16)	72	(18)	
III	6	(3)	20	(5)	
IV	12	(7)	39	(10)	
V	43	(24)	91	(23)	
Missing	2	(1)	10	(3)	
Modified Fisher grade					0.76
0	2	(1)	7	(2)	
1	17	(10)	32	(8)	
2	8	(4)	9	(3)	
3	36	(20)	74	(19)	
4	100	(56)	219	(58)	
Missing	16	(9)	61	(11)	
Type of intervention					0.65
Clipping	57	(39)	126	(37)	
Coiling	88	(60)	208	(61)	
Both coiling and clipping	2	(1)	2	(1)	
Not treated	32	(17)	59	(14)	
Missing	0	(0)	3	(0.75)	
Discharge destination					0.36
Home	73	(41)	138	(35)	
Rehabilitation	58	(32)	148	(37)	
Death	48	(27)	108	(27)	
Unknown	0	(0)	4	(1)	

WFNS World Federation of Neurological Surgeons grading

[§] Number and (%), unless otherwise indicated

Aneurysm characteristics

In both sexes, aneurysms were more common in the anterior than posterior circulation (Table 2, Fig. 1). There were more midline aneurysms in men (42%) than women (31%) and more left sided aneurysms in women (24%) than men (32%). There were sex differences in the anatomical location of aneurysm ($p = 0.001$). Anterior cerebral artery location (42%) was the most common site in men followed by middle cerebral artery (20%) and posterior circulation (20%). In women, anterior cerebral artery (33%), posterior communicating artery (20%) and posterior circulation (20%) were the

Table 2 Sex differences in aneurysm-specific findings

Aneurysm specific findings	Men[§] N = 179		Women[§] N = 398		P value
	N	%	N	%	
Aneurysm identified	172	(94)	376	(94)	
Posterior or anterior					0.27
Posterior	38	(21)	64	(16)	
Anterior	134	(75)	313	(79)	
Unknown	7	(4)	21	(5)	
Side of aneurysm					0.03*
Right	54	(30)	123	(31)	
Left	43	(24)	129	(32)	
Midline	75	(42)	124	(31)	
Unknown	7	(4)	22	(6)	
Location of aneurysm[¶]					0.001*
Pcomm	13	(7)	81	(20)	
Internal Carotid	12	(6)	37	(9)	
ACho	2	(1)	7	(2)	
ICA	10	(5)	30	(7)	
Anterior cerebral	74	(42)	129	(33)	
ACA-A1	5	(3)	20	(5)	
ACA-Acomm	64	(36)	94	(24)	
ACA-pericallosal	5	(3)	15	(4)	
Middle cerebral	36	(20)	65	(16)	
MCA-M1	17	(9)	25	(6)	
MCA-at bifurcation	18	(10)	35	(9)	
MCA-distal MCA	1	(0.5)	5	(1)	
Posterior circulation	37	(20)	66	(20)	
PCA-distal	2	(1)	0	(0)	
P2	2	(1)	0	(0)	
P1	0	(0)	1	(0.5)	
Basilar bifurcation	13	(7)	26	(6)	
SCA	3	(2)	2	(0.5)	
Basilar trunk	5	(3)	9	(2)	
AICA	0	(0)	1	(0.25)	
V-B junction	1	(0.5)	1	(0.25)	
Vertebral	3	(2)	10	(2)	
PICA	8	(4)	16	(4)	
Other	0	(0)	0	(0)	
Choroidal	0	(0)	0	(0)	
Unknown	7	(4)	19	(5)	
Size of aneurysm (mean ± SD) mm	7.89(±4.65)		6.93(±4.14)		0.02*
Missing	11	(6)	30	(7)	
Categories of size (mm)					0.03*
≤6.9	83	(46)	214	(54)	
7–9.9	37	(21)	88	(22)	
10–19.9	42	(23)	61	(15)	
≥20	6	(3)	5	(1)	

[§] Number and (%), unless otherwise indicated

[¶] Aneurysm location collapsed to five categories as mentioned in the text

Posterior communicating, *Pcomm*; anterior choroidal, *ACho*; internal carotid artery, *ICA*; anterior cerebral artery, *ACA*; anterior communicating artery, *Acomm*; pre-communicating part of ACA, *A1*; middle cerebral artery, *MCA*; sphenoidal segment of MCA, *M1*; posterior cerebral artery, *PCA*; precommunicating part of PCA, *P1*; postcommunicating part of PCA, *P2*; superior cerebellar artery, *SCA*; anterior inferior cerebellar artery, *AICA*; vertebrobasilar junction, *V-B junction*; posterior inferior cerebellar artery, *PICA*
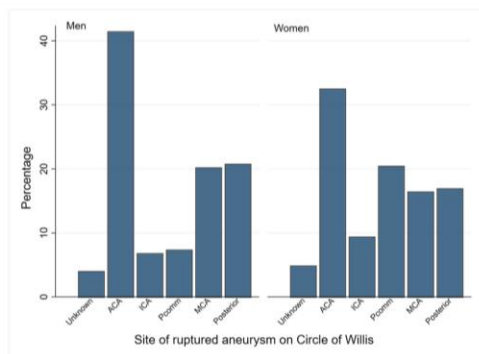
Fig. 1 Distribution of Aneurysm site in men and women. Posterior communicating, Pcomm. Internal carotid artery, ICA. Anterior cerebral artery, ACA. Middle cerebral artery, MCA. Posterior circulation aneurysms, Posterior

most common positions for the rupture of the aneurysm. The mean size of aneurysm was smaller in women than men ($p = 0.02$). More men (26%) than women (16%, $p = 0.03$) had an aneurysm size > 10 mm.

Aneurysmal repair

Aneurysm was repaired by either clipping or coiling or both. There was no sex difference in the type of intervention (Table 1).

Complications

Neurological complications were common, with 61% of men and 69% of women having at least one complication (Table 3). We were unable to detect a difference between men and women in post-operative stroke within 48 h, early rebleeding and after intervention, seizure, meningitis, cerebral infarction and ventriculitis. Hydrocephalus (men 46%, women 54%, $p = 0.06$) and DCI were less common in men compared with women (men 25%, women 35%, $p = 0.003$).

Treatment for DCI

In total, 130 (33%) women and 42 (23%) men experienced DCI. Among those with DCI, women (55%) more often received treatment than men (40%; $p = 0.08$, Table 3). A total of 71 (55%) women and 17 (40%) men with confirmed DCI and/ or cerebral infarction received some type of endovascular management. Among these, more women (93%) received intraarterial vasodilators (nicardipine, papaverine and nimodipine) than men (65%). Mechanical treatment of endovascular angioplasty was more common in men (35%) than women (7%, $p = 0.001$).

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Treatment for hydrocephalus

Ventriculostomy was performed in 46% men and 54% women ($p = 0.06$), while shunt placement was conducted in 7% of men and 12% of women ($p = 0.22$; Table 3).

Sex differences in poor outcome

Regarding sex differences in outcome, more men (40.7%) went home compared to women (34.6%) while more women were discharged to rehabilitation (men 32.4% vs women 37.1%) or died in-hospital (men 26.8% vs women 27.1%).

In univariable analysis including all people with aSAH, women compared with men had a marginally greater risk of being discharged to rehabilitation (RRR 1.15 95% CI 0.90–1.48) and similar likelihood of in-hospital death (RRR 1.02 95% CI 0.76–1.36) versus being discharged to home (Table 4). Potential prestroke confounding factors and covariates of aneurysm characteristics and neurological complications that were different between the sexes were analysed for association with the outcome. Age, DCI and hydrocephalus were associated with discharge to rehabilitation and in hospital death while hypertension history and size of the aneurysm were associated with in-hospital death only. We identified that age, hypertension history and smoking status were different between men and women, whereas, severity scores, comorbidities and treatment modalities were similar between the sexes. In model 1, adjusted for prestroke confounding factors (Table 4), women compared with men had a marginally greater risk of being discharged to rehabilitation (1.13 95% CI 0.87–1.48, $p = 0.34$) and lesser risk of in-hospital death (0.75 95% CI 0.51–1.10, $p = 0.14$). In model 2 (Table 4), adjusted for covariates (DCI and hydrocephalus), women had a somewhat lesser risk of being discharged to rehabilitation (0.87 95% CI 0.69–1.11, $p = 0.28$) and death (0.80 95% CI 0.52–1.23, $p = 0.32$) where age, hypertension history, presence of DCI and hydrocephalus were independently associated with death and discharge to rehabilitation. There were no interactions between sex and the other variables included in the final model.

In the sensitivity analyses on the matched analysis of men and women (Table 5), the relative risk ratio for discharge to rehabilitation was 1.19 (95% CI 0.75–1.89, $p = 0.44$) and for in-hospital death was 0.84 (95% CI 0.48–1.48, $p = 0.56$). In covariate adjusted analysis, the risk of discharge to rehabilitation was 0.84 (95% CI 0.50–1.39, $P = 0.50$), and the risk of death was 0.73 (95% CI 0.40–1.33, $p = 0.31$). There were slight differences in the risk, but the confidence intervals were wide. The estimates were nearly consistent with log multinomial regression.

Regarding missing data, an analysis of the characteristics associated with missing data showed that only the proportion dying during hospitalisation differed between those with and

Table 3 Complications following aSAH

Complications	Men[§] N = 179		Women[§] N = 398		P value
	N	%	N	%	
Any neurological complication					0.05*
Yes	110	(61)	275	(69)	
No	69	(39)	119	(30)	
Missing	0	(0)	4	(1)	
Postop stroke within 48 h					0.59
Yes	34	(19)	66	(17)	
No	144	(80)	322	(81)	
Unknown	1	(1)	10	(3)	
Early or before treatment rebleed					0.94
Yes	14	(8)	30	(8)	
No rebleed	165	(92)	362	(91)	
Unknown	0	(0)	6	(1)	
Rebleed after treatment					0.42
Yes, confirmed/suspected	3	(2)	9	(3)	
No rebleed	175	(97)	381	(95)	
Unknown	1	(1)	8	(2)	
Hydrocephalus					0.06
Yes	83	(46)	215	(54)	
No	95	(53)	176	(44)	
Unknown	1	(1)	7	(2)	
DCI (clinical deterioration)					0.003**
Yes	34	(19)	122	(31)	
No	135	(75)	253	(64)	
Unknown	10	(6)	23	(5)	
Cerebral infarction					0.51
Yes	35	(20)	85	(21)	
No	137	(76)	287	(72)	
Unknown or missing	7	(4)	26	(6)	
Neurological infection					0.24
Meningitis/ventriculitis	14	(8)	43	(11)	
Non-neurological infections or no infection	164	(92)	346	(87)	
Unknown	1	(1)	9	(2)	
Seizure					0.37
Yes	12	(7)	28	(7)	
No	165	(92)	358	(90)	
Unknown	2	(1)	12	(3)	
Management of complications					
Endovascular therapy for DCI/cerebral infarction[†]					0.08
No	24	(57)	54	(41)	
Yes	17	(40)	71	(55)	
Missing	1	(2)	5	(4)	
Type of endovascular intervention for DCI/cerebral infarction					0.001 **
Balloon angioplasty	6	(35)	5	(7)	
Intraarterial vasodilator	11	(65)	66	(93)	
Ventriculostomy					0.06
Yes	82	(46)	213	(54)	

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Table 3 (continued)

Complications	Men[§] N = 179		Women[§] N = 398		P value
	N	%	N	%	
No	97	(54)	179	(45)	
Missing	0	(0)	6	(1)	
Shunt placement					0.22
Yes	13	(7)	46	(12)	
No	163	(91)	342	(86)	
Missing	3	(2)	10	(2)	

[§] Number and (%), unless otherwise indicated

[†] n = 42 men and n = 130 women had DCI and/or cerebral infarction

[††] Denominator is n = 17 men and n = 71 women with endovascular intervention for DCI/cerebral infarction

without data on complications or details of the aneurysm (Online Resource Supplementary Tables 1–3).

Discussion

This is the largest study examining the role of sex in short term-outcome following aSAH. Women were older; more often had a history of hypertension and more frequently suffered from DCI and hydrocephalus than men. Sex did not predict outcome however women had a marginally greater risk of being discharged to rehabilitation and in-hospital death. The risk of death decreased slightly when prestroke confounding factors were taken into account. The risk of poor outcomes in women was explained by age, history of hypertension, presence of DCI and hydrocephalus.

Sex did not predict poor outcomes in our study. Among the few prior studies designed to examine the factors associated with the outcome in aSAH, women have generally been found to have a poorer outcome than men [8, 46], although not consistently [10, 12, 20]. In one comparable study of 120 people (69% women), although 6-month mortality appeared to be greater in women (28%) than men (16%), this was not apparent in multivariable analysis [10]. In other studies, there was no detectable difference between men and women in the risk of worse outcome at 3 months when adjusting for age, neurological condition on admission, site [12, 20] and size of aneurysm, and length of stay [20]. There is an urgent need for research to improve diagnosis, prevention and treatment of complications after aSAH, particularly DCI and management of hydrocephalus, which could lead to improved outcome.

DCI and hydrocephalus were more common in women than in men. Our finding is in agreement with some studies [11, 17, 38] but contrasts with others [33, 41]. The risk of DCI is associated with the size of initial bleed and poor WFNS grades [14], but its pathophysiology remains unexplained [36]. The greater risk of DCI in women could be related to

physiological factors including smaller vessels compared with men that result in high sheer wall stress inducing vascular injury and ultimately leading to ischemia [17]. The explanation for our finding that hydrocephalus was more common in women than men is unclear, but some authors suggest a possible role of oestrogen [39]. Complications were very common after aSAH, and there are limited clinical guidelines to guide prevention, diagnosis and management.

There were sex differences in the location of ruptured aneurysms. The anterior communicating artery was the most common site in men, while anterior communicating and posterior communicating arteries were the most common locations in women. This is consistent with previous studies that tended to be single-centre or regionally focused [1, 18, 20]. These sex differences in aneurysm site on Circle of Willis may be due to morphological, embryological and physiological factors. In a study based on sex differences specific to morphology of ruptured aneurysms of anterior communicating artery, the authors noticed that morphological measures of the aneurysm such as aneurysm size, flow angles and vessel angles were greater in men than women [26]. These morphological differences might be the reason for more anterior communicating ruptured aneurysms in men than women [26]. Anatomical variations in the Circle of Willis, which are linked to a higher rate of aneurysm rupture, have been linked to differences in aneurysm distribution in men and women [22]. Type A variation when there is an absence of unilateral A1 segment (precommunicating part of anterior cerebral artery) was more common in men, while women more often had type P variations when the foetal type of posterior cerebral artery originates from the internal carotid artery, and thus has been linked to internal carotid artery aneurysm [23].Considering physiological factors, authors of another study found that vessel diameters were greater in men than in women. There was more sheer wall stress in women [45] mostly at bifurcations, and this could be a

Table 4 Relative risk ratio for discharge home or rehabilitation versus death in women compared with men in log multinomial regression analysis

Variables	All patients $N = 577$					
	Rehabilitation			Death		
	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)	Unadjusted RRR (95% CI)	Model 1 RRR (95%CI)	Model 2* RRR (95%CI)
Female sex	1.15 (0.90–1.48)	1.13 (0.87–1.48)	0.87 (0.69–1.11)	1.02 (0.76–1.36)	0.75 (0.51–1.10)	0.80 (0.52–1.23)
Aneurysm characteristics						
Site						
Anterior cerebral	Ref			Ref		
Internal carotid	0.98 (0.65–1.48)			1.40 (0.85–2.30)		
Posterior communicating	0.83 (0.58–1.18)			1.12 (0.72–1.74)		
Middle cerebral	0.99 (0.72–1.34)			1.36 (0.91–2.03)		
Posterior circulation	1.12 (0.83–1.50)			1.36 (0.91–2.03)		
Size of aneurysm (mm)	0.99 (0.96–1.01)			*1.04 (1.02–1.05)*		
Neurological complications						
Hydrocephalus	*2.50 (1.91–3.27)*		*1.68 (1.27–2.23)*	*1.71 (1.27–2.29)*		*1.97 (1.27–3.05)*
DCI (Clinical deterioration)	*2.72 (2.20–3.36)*		*2.80 (2.02–3.90)*	*0.63 (0.42–0.91)*		0.95 (0.53–1.69)
Confounding factors						
Age	*1.00 (0.99–1.02)*	*1.01 (0.99–1.02)*	*1.01 (1.00–1.02)*	*1.01 (1.01–1.02)*	*1.02 (1.01–1.04)*	*1.04 (1.02–1.06)*
Smoking						
Non-smoker	Ref	Ref				
Current smoker	0.97 (0.73–1.26)	1.06 (0.79–1.42)	0.87 (0.70–1.09)	0.89 (0.57–1.37)	1.16 (0.74–1.81)	1.51 (0.90–2.55)
Ex-smoker	1.09 (0.76–1.58)	1.19 (0.81–1.73)	1.05 (0.73–1.51)	0.87 (0.46–1.65)	0.93 (0.49–1.77)	0.79 (0.41–1.51)
Hypertension						
No	Ref	Ref				
Yes	1.15 (0.89–1.38)	0.99 (0.78–1.27)	*1.33 (1.05–1.70)*	*1.81 (1.35–2.41)*	*1.61 (1.12–2.33)*	*1.85 (1.17–2.91)*

Model 1 (adjusted for pre-stroke confounding factors)

Model 2 (adjusted for pre-stroke confounding factors and covariates)

*Adjusted for hospital network

Confounders included age, hypertension history and smoking status and covariates included DCI and hydrocephalus, $p < 0.05$ italicized

potential reason for more aneurysms in women. Although posterior circulation aneurysms and greater aneurysmal size were considered predictors of unfavourable outcomes in previous studies [34, 44], in our study, most aneurysms were located in the anterior circulation. Despite the sex differences in location and size of the ruptured aneurysm, we could not detect any association of these findings with outcome in the covariate adjusted analyses.

Although our study was focused on sex differences in aSAH, the study also provides more general insights into predictors of poor outcome after aSAH from a large, multicentre, contemporary cohort ascertained using sound epidemiological methods. We observed that risk factors like history of hypertension were more common in women, and smoking was more frequent in men. A poor risk factor profile leads to early deaths from aSAH [27]. These behavioural factors have been

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Table 5 Relative risk ratio for discharge home or rehabilitation versus death in women compared to men in multinomial logistic regression analysis with propensity score matching

Variables	All patients $N = 577$			
	Rehabilitation		Death	
	RRR (95% CI) *	RRR (95% CI) **	RRR (95% CI) *	RRR (95% CI) **
Female sex	1.19 (0.75–1.89)	0.84 (0.50–1.39)	0.84 (0.48–1.48)	0.73 (0.40–1.33)
Hydrocephalus		*4.14 (2.47–6.94)*		*3.16 (1.75–5.69)*
DCI (clinical deterioration)		*6.00 (3.13–11.49)*		1.94 (0.92–4.08)

*Matched on pre-stroke confounders different by sex

**Adjusted for covariates and hospital network

Confounders included age, hypertension history and smoking status and covariates included DCI and hydrocephalus, $p < 0.05$ italicized

linked to unfavourable outcomes [9, 28] and are also a cause of various neurological complications after aSAH [9, 13, 24]. Older age was also a risk for worse outcomes in our study as supported by others [15, 34]. In accordance with previous research, patients with DCI [37] and hydrocephalus [2, 3] were more often discharged to rehabilitation, an indicator of greater functional impairment, and had a greater risk of in-hospital death, reinforcing the significance of these complications. Prevention of modifiable risk factors and rapid diagnosis and improvement in the management of DCI and hydrocephalus are important to prevent death and temporary or permanent disability after aSAH in both sexes but, particularly, in women given their higher incidence rate in that group.

There were some limitations of our study. Owing to the low incidence of aSAH, the study was retrospective, which resulted in some missing data for the outcomes of interest ($\leq 10\%$) and risk factors like smoking (25%). As out of hospital deaths were not available for the study, our results are only generalizable to hospitalized patients. The use of discharge outcome is also a limitation of our study, as functional improvement or deterioration from delayed complications may occur following discharge. Examination of other more relevant patient-centred outcomes such as health related quality of life is needed. We also did not have data on severity of angiographic vasospasm which is one of the mechanisms that leads to DCI [6]. Instead, we recorded DCI using the clinical NINDS definition noting that 'vasospasm' was often used as an alternate term in medical records. We recorded for hydrocephalus indicated by intervention like ventriculostomy or shunt placement. We further confirmed DCI and hydrocephalus from postoperative notes, imaging and details on treatment related to both complications. Aneurysm characteristics were taken from neuroimaging after rupture, which may result in misestimation of aneurysm size, noting that this is a common method used in studies of aSAH [18, 20].

There were several strengths of the current study. Unlike most previous studies that have been in single centres, we had data from all consecutive cases of radiographically confirmed aSAH across two hospital networks, making our results more generalizable. We had access to clinical and radiological records and only included confirmed cases of aneurysmal rupture. We further included only first ever cases of aSAH, and so our findings were not complicated by ongoing neurological impairments from previous events, different management or outcomes. We used standardised clinical definitions for complications, while aneurysm characteristics were reported by neuroradiologists.

Conclusions

In conclusion, women were overrepresented in our cohort of people with aSAH. They were older, and more often have a history of hypertension whereas smoking was more common in men. They were found to have a slightly greater likelihood of being discharged to rehabilitation and in-hospital death compared with men, but this was explained by older age, hypertension history, presence of DCI and hydrocephalus. Better management of behavioural risk factors and neurological complications could overall improve the outcomes.

Compliance with ethical standards

Conflict of interest   The authors declare that they have no conflict of interest.

Ethical approval   This study was approved by the Human Research Ethics Committee in Victoria (RES-18-0000-036A) and Tasmania (H0014563). For this retrospective study formal consent is not required.

Disclaimer   The sponsor had no role in the design or conduct of this research.

References

1. Aarhus M, Helland CA, Wester K (2009) Differences in anatomical distribution, gender, and sidedness between ruptured and unruptured intracranial aneurysms in a defined patient population. Acta Neurochir 151:1569. https://doi.org/10.1007/s00701-009-0316-3

2. Adams H, Ban VS, Leinonen V, Aoun SG, Huttunen J, Saavalainen T, Lindgren A, Frosen J, Fraunberg M, Koivisto T, Hernesniemi J, Welch BG, Jaaskelainen JE, Huttunen TJ (2016) Risk of shunting after aneurysmal subarachnoid hemorrhage. Stroke 47:2488–2496. https://doi.org/10.1161/STROKEAHA.116.013739

3. Awe OO, Gonzalez LF, Hasan D, Maltenfort M, Rossenwasser R, Jabbour P (2011) Treatment outcome of aneurysmal subarachnoid hemorrhage in patients aged 70 years and older. Neurosurg 68:753–758. https://doi.org/10.1227/NEU.0b013e318207a9fb

4. Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, Corniola M-V, Perren F, Rüfenacht D, Schaller K (2017) PHASES score for the management of intracranial aneurysm: a cross-sectional population-based retrospective study. Stroke 48:2105–2112

5. Buczacki S, Kirkpatrick P, Seeley H, Hutchinson P (2004) Late epilepsy following open surgery for aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 75:1620–1622

6. Budohoski KP, Guilfoyle M, Helmy A, Huuskonen T, Czosnyka M, Kirollos R, Menon DK, Pickard JD, Kirkpatrick PJ (2014) The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 85:1343–1353

7. Cha KC, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS (2010) Aneurysmal rebleeding: factors associated with clinical outcome in the rebleeding patients. J Korean Neurosurg Soc 47:119

8. Chotai S, Ahn SY, Moon HJ, Kim JH, Chung HS, Chung YG, Kwon TH (2013) Prediction of outcomes in young adults with aneurysmal subarachnoid hemorrhage. Neurol Med Chir 53:157–162

9. D'Souza S (2015) Aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 27:222

10. De Marchis GM, Schaad C, Fung C, Beck J, Gralla J, Takala J, Jakob SM (2017) Gender-related differences in aneurysmal subarachnoid hemorrhage: a hospital based study. Clin Neurol Neurosurg Clinical Neurology and Neurosurgery 157:82–87. https://doi.org/10.1016/j.clineuro.2017.04.009

11. Duan W, Pan Y, Wang C, Wang Y, Zhao X, Wang Y, Liu L (2018) Risk factors and clinical impact of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: analysis from the China National Stroke Registry. Neuroepidemiology 50:128–136. https://doi.org/10.1159/000487325

12. Duijghuisen JJ, Greebe P, Nieuwkamp DJ, Algra A, Rinkel GJ (2016) Sex-related differences in outcome in patients with aneurysmal subarachnoid hemorrhage. J Stroke and Cerebrovasc Dis 25:2067–2070

13. Ferguson S, Macdonald RL (2007) Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. Neurosurg 60:658–667

14. Francoeur CL, Mayer SA (2016) Management of delayed cerebral ischemia after subarachnoid hemorrhage. Crit Care 20:277. https://doi.org/10.1186/s13054-016-1447-6

15. Galea JP, Dulhanty L, Patel HC (2017) Predictors of outcome in aneurysmal subarachnoid hemorrhage patients: observations from a multicenter data set. Stroke 48:2958–2963

16. Gall S, Donnan G, Dewey H, Macdonell R, Sturm J, Gilligan A, Srikanth V, Thrift A (2010) Sex differences in presentation, severity, and management of stroke in a population-based study. Neurology 74:975–981

17. Germans MR, Jaja BN, de Oliviera Manoel AL, Cohen AH, Macdonald RL (2018) Sex differences in delayed cerebral ischemia after subarachnoid hemorrhage. J Neurosurg 129:458–464

18. Ghods AJ, Lopes D, Chen M (2012) Gender differences in cerebral aneurysm location. Front Neurol 3:78

19. Greenland S (1989) Modeling and variable selection in epidemiologic analysis. Am J Public Health 79:340–349

20. Hamdan A, Barnes J, Mitchell P (2014) Subarachnoid hemorrhage and the female sex: analysis of risk factors, aneurysm characteristics, and outcomes. J Neurosurg 121:1367–1373

21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381. https://doi.org/10.1016/j.jbi.2008.08.010

22. He Z, Wan Y (2018) Is fetal-type posterior cerebral artery a risk factor for intracranial aneurysm as analyzed by multislice CT angiography? Exp Ther Med 15:838–846

23. Horikoshi T, Akiyama I, Yamagata Z, Sugita M, Nukui H (2002) Magnetic resonance angiographic evidence of sex-linked variations in the circle of Willis and the occurrence of cerebral aneurysms. J Neurosurg 96:697. https://doi.org/10.3171/jns.2002.96.4.0697

24. Horiuchi T, Tanaka Y, Hongo K (2006) Sex-related differences in patients treated surgically for aneurysmal subarachnoid hemorrhage. Neurol Med Chir 46:328–332

25. Kongable GL, Lanzino G, Germanson TP, Truskowski LL, Alves WM, Torner JC, Kassell NF (1996) Gender-related differences in aneurysmal subarachnoid hemorrhage. J Neurosurg 84:43–48

26. Lin B, Chen W, Ruan L, Chen Y, Zhong M, Zhuge Q, Fan LH, Zhao B, Yang Y (2016) Sex differences in aneurysm morphologies and clinical outcomes in ruptured anterior communicating artery aneurysms: a retrospective study. BMJ Open 6:e009920. https://doi.org/10.1136/bmjopen-2015-009920

27. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M (2017) Risk factors of sudden death from subarachnoid hemorrhage. Stroke 48:2399–2404. https://doi.org/10.1161/STROKEAHA.117.018118

28. Lindbohm JV, Kaprio J, Korja M (2019) Survival bias explains improved survival in smokers and hypertensive individuals after aSAH. Neurology 93:e2105–e2109

29. Nichols L, Stirling C, Otahal P, Stankovich J, Gall S (2018) Socioeconomic disadvantage is associated with a higher incidence of aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 27:660–668. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.055

30. Nieuwkamp DJ, Vaartjes I, Algra A, Bots ML, Rinkel GJ (2013) Age-and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the Netherlands. Int J Stroke 8:90–94

31. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, Heeley E, Otahal P, Konstantinos V, Anderson C (2017) Sex

differences in long-term mortality after stroke in the INSTRUCT (INternational STRoke oUtComes sTudy) a meta-analysis of individual participant data. Circ Cardiovasc Qual Outcomes 10: e003436

32. Rodríguez DR, Matamoros CS, Cúe LF, Hernández JM, Sánchez YP, Nellar JP (2017) Factors associated with poor outcome for aneurysmal subarachnoid haemorrhage in a series of 334 patients. Neurología (English Edition) 32:15–21

33. Rooij NK, Rinkel GJE, Dankbaar JW, Frijns CJM (2013) Delayed cerebral ischemia after subarachnoid hemorrhage. Stroke 44:43–54. https://doi.org/10.1161/STROKEAHA.112.674291

34. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL (2007) Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. Stroke 38:2315–2321

35. Rosenørn J, Eskesen V, Schmidt K (1993) Clinical features and outcome in females and males with ruptured intracranial saccular aneurysms. Br J Neurosurg 7:287–290

36. Rowland M, Hadjipavlou G, Kelly M, Westbrook J, Pattinson K (2012) Delayed cerebral ischaemia after subarachnoid haemorrhage: looking beyond vasospasm. Br J Anaesth 109:315–329

37. Sanelli PC, Anumula N, Gold R, Elias E, Johnson C, Comunale J, Tsiouris AJ, Segal AZ (2012) Outcomes-based assessment of a new reference standard for delayed cerebral ischemia related to vasospasm in aneurysmal subarachnoid hemorrhage. Acad Radiol 19: 1066–1074

38. Sheehan JP, Polin RS, Sheehan JM, Baskaya MK, Kassell NF (1999) Factors associated with hydrocephalus after aneurysmal subarachnoid hemorrhage. Neurosurg 45:1120–1128

39. Shishido H, Zhang H, Okubo S, Hua Y, Keep RF, Xi G (2016) The effect of gender on acute hydrocephalus after experimental subarachnoid hemorrhage. In: Brain Edema XVI. Springer, pp 335–339

40. Suarez JI, Sheikh MK, Macdonald RL, Amin-Hanjani S, Brown RD, de Oliveira Manoel AL, Derdeyn CP, Etminan N, Keller E, Leroux PD, Mayer SA, Morita A, Rinkel G, Rufennacht D, Stienen MN, Torner J, Vergouwen MDI, Wong GKC, Suarez JI, Macdonald RL, Amin-Hanjani S, Brown RD, de Oliveira Manoel AL, Derdeyn CP, Etminan N, Keller E, LeRoux PD, Mayer S, Morita A, Rinkel G, Rufennacht D, Stienen MN, Torner J, Vergouwen MDI, Wong GKC, Bijlenga P, Ko N, McDougall CG, Mocco J, Murayama Y, Werner MJH, Broderick J, Dhar R, Jauch EC, Kirkpatrick PJ, Martin RH, Mocco J, Muehlschlegel S, Mutoh T, Nyquist P, Olson D, Mejia-Mantilla JH, van der Jagt M, Bambakidis NC, Brophy G, Bulsara K, Claassen J, Connolly ES,

Hoffer SA, Hoh BL, Holloway RG, Kelly A, Nakaji P, Rabinstein A, Vajkoczy P, Woo H, Zipfel GJ, Chou S, Doré S, Dumont AS, Gunel M, Kasuya H, Roederer A, Ruigrok Y, Vespa PM, Sarrafzadeh-Khorrasani AS, Hackenberg K, Huston J, Krings T, Lanzino G, Meyers PM, Wintermark M, Daly J, Ogilvy C, Rhoney DH, Roos YB, Siddiqui A, Algra A, Frösen J, Hasan D, Juvela S, Langer DJ, Salman RA-S, Hanggi D, Schweizer T, Visser-Meily J, Amos L, Ludet C, Moy C, Odenkirchen J, Ala'i S, Esterlitz J, Joseph K, Sheikh M, Aneurysms tUI, Investigators SCP (2019) Common data elements for unruptured intracranial aneurysms and subarachnoid hemorrhage clinical research: a National Institute for Neurological Disorders and Stroke and National Library of Medicine Project. Neurocrit Care 30:4–19. https://doi.org/10.1007/s12028-019-00723-6

41. Vale FL, Bradley EL, Fisher WS 3rd (1997) The relationship of subarachnoid hemorrhage and the need for postoperative shunting. J Neurosurg 86:462–466. https://doi.org/10.3171/jns.1997.86.3.0462

42. Vergouwen MD, Ilodigwe D, Macdonald RL (2011) Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and-independent effects. Stroke 42:924–929

43. Wáng YXJ, He J, Zhang L, Li Y, Zhao L, Liu H, Yang L, Zeng XJ, Yang J, Peng GM, Ahuja A, Yang ZH (2016) A higher aneurysmal subarachnoid hemorrhage incidence in women prior to menopause: a retrospective analysis of 4,895 cases from eight hospitals in China. Quant Imaging Med Surg 6:151–156. https://doi.org/10.21037/qims.2016.01.06

44. Wouter IS, Eelco FMW, David GP, Chu-Pin C, O'Fallon WM, Jack PW (1995) The poor prognosis of ruptured intracranial aneurysms of the posterior circulation. J Neurosurg 82:791–795. https://doi.org/10.3171/jns.1995.82.5.0791

45. Zhao X, Zhao M, Amin-Hanjani S, Du X, Ruland S, Charbel FT (2015) Wall shear stress in major cerebral arteries as a function of age and gender—a study of 301 healthy volunteers. J Neuroimaging 25:403–407. https://doi.org/10.1111/jon.12133

46. Zheng K, Zhong M, Zhao B, Chen S-Y, Tan X-X, Li Z-Q, Xiong Y, Duan C-Z (2019) Poor-grade aneurysmal subarachnoid hemorrhage: risk factors affecting clinical outcomes in intracranial aneurysm patients in a multi-center study. Front Neurol 10:123

Appendix E: REDDISH STUDY-Database and Data Dictionary information

Patient Information

Variable / Field Name	Record_id
Form Name	patient_information
Field Type	Text
Field Label	Record ID
rSource	This will automatically populate
Further description	This field is the auto-populated record ID prescribed by REDcap

Variable / Field Name	Name
Form Name	patient_information
Field Type	Text
Field Label	Name
Identifier?	Yes
Branching Logic (Show field only if...)	No
Required Field?	Yes
Source	Individual patient medical records, admission form or patient administrative system.
Further description	First name Last name The format in which it is written should be the same as that indicated by the person (e.g. written on a form) or in the same format as that printed on an identification card, such as a Medicare card, to ensure consistent collection of name data. - In instances where the person has a number of different names and there is uncertainty about which name to record for a person, please record the person's name as it appears on their Medicare card. - Some people do not have a family name and a given name; they have only one name by which they are known.

Variable / Field Name	Mrn
Form Name	patient_information
Field Type	Text
Field Label	Medical Record Number (MRN)/ UR number
Identifier?	Yes
Required Field?	Yes
Source	Individual patient medical records – the numbering system including the content and format of the medical record number is usually specific to the individual health care service. This is the THCI number for Tasmanian Patients
Further description	The MRN is collected to assist in individual patient identification and to identify potential duplicates in the database. It is the current method of patient identification being used for purposes such as delivery of care, record keeping and communication.

Variable / Field Name	**Gender**
Form Name	patient_information
Field Type	Radio
Field Label	Gender
Choices, Calculations	1, Male | 2, Female | 3, intersex or indeterminate
Required Field?	Yes
Source	Individual patient medical records, admission form or patient administrative system.
Further description	Sex will be captured as it is written in the medical record. If there is a conflict, document the self-identified gender.

Variable / Field Name	**Dob**
Form Name	patient_information
Field Type	text
Field Label	Date of birth
Field Note	The date of birth of the person.
Text Validation Type	DD-MM-YYYY
Required Field?	yes
Identifier?	Yes
Source	Individual patient medical records, admission form or patient administrative system.
Further description	If day of birth is unknown, use 01 for the day (01/MM/YYYY). - If the day and month of birth are unknown, use 01 for the day and month (01/01/YYYY). - If the date of birth is unknown, estimate the client's age in years and subtract this from the current year (01/01/YYYY).

Variable / Field Name	**postcode**
Form Name	patient_information
Field Type	text
Field Label	Postcode
Field Note	Postcode for place of residence
Text Validation Type	postalcode_australia
Required Field?	yes
Source	Individual patient medical records, admission form or patient administrative system, ambulance report
Further description	This is the postcode of the patient's residential address at the time of the event. (not the current postcode). The numeric descriptor for a postal delivery area, aligned with locality, suburb or place for the address of a person. Leave blank when the locality name or geographic area for a person is not known, or when a person has no fixed address. - For person's visiting from overseas, record their local Australian address.

Variable / Field Name	**suburb**
Form Name	patient_information
Field Type	text
Field Label	Suburb
Field Note	Suburb for place of residence
Required Field?	yes

Source	Individual patient medical records, admission form or patient administrative system, ambulance report
Further description	This is the suburb of the patient's residential address at the time of the event. (not the current suburb). The full name of the locality contained within the specific address of a person, as represented by text. The suburb name may be a town, city, suburb or commonly used location name such as a large agricultural property or Aboriginal community. - Leave blank when the locality name or geographic area for a person is not known, or when a person has no fixed address. - For person's visiting from overseas, record their local Australian address.

Variable / Field Name	**marital_status**
Form Name	patient_information
Field Type	Radio
Field Label	Marital status
Choices, Calculations	1, Married (de facto) | 2, Never married (single) | 3, Widowed | 5, Unknown
Required Field?	Yes
Source	Individual patient medical records, admission form or patient administrative system
Further description	A de facto relationship is defined in Section 4AA of the *Family Law Act 1975*. The law requires that you and your former partner, who may be of the same or opposite sex, had a relationship as a couple living together on a genuine domestic basis.

Variable / Field Name	**priv_health_ins**
Form Name	patient_information
Field Type	Radio
Field Label	Private Health Insurance
Choices, Calculations	1, Yes 2, No 3, Unknown 4, Department of Veteran Affairs (DVA)
Required Field?	Yes
Source	Individual patient medical records, admission form or patient administrative system
Further description	Does the patient have private health insurance? http://meteor.aihw.gov.au/content/index.phtml/itemId/352427

Variable / Field Name	**indigenous_status**
Form Name	patient_information
Field Type	Radio
Field Label	Indigenous Status
Choices, Calculations, OR Slider Labels	1, Aboriginal 2, Torres Strait Islander 3, Both Aboriginal and Torres Strait Islander 4, Neither Aboriginal nor Torres Strait Islander 5, Unknown
Required Field?	Yes
Source	Individual patient medical records, admission form or patient administrative system.

	Australian Indigenous status will be captured as it is written in the medical record. If there is a conflict, document with the self-identified origin, i.e. origin as reported by the person.
Further description	Rationale: Indigenous Australians suffer poorer health outcomes than their counterparts. Stroke subtypes also vary by different ethnic status, as well as risk factor prevalence

Variable / Field Name	**Height**
Form Name	patient_information
Field Type	Text
Field Label	Height
Field Note	enter in cm e.g. 175cm
Text Validation Min	120
Text Validation Max	220
Required Field?	Yes
Source	
Further description	Leave blank if unavailable Rounding to the nearest 1 cm will be required http://meteor.aihw.gov.au/content/index.phtml/itemId/270365

Variable / Field Name	**Weight**
Form Name	patient_information
Field Type	text
Field Label	Weight
Field Note	enter in kg
Text Validation Type OR Show Slider Number	number
Text Validation Min	40
Text Validation Max	300
Required Field?	yes
Source	
Further description	Leave blank if unavailable The measurement is recorded to the nearest 0.1 kg http://meteor.aihw.gov.au/content/index.phtml/itemId/270208

Inclusion/Exclusion criteria

Variable / Field Name	**incl_exc**
Form Name	inclusionexclusion_criteria
Field Type	radio
Field Label	Is this event an aSAH?
Choices, Calculations, OR Slider Labels	1, Confirmed - aSAH confirmed on neuroimaging and/or lumbar puncture 2, Probable - aSAH suspected but definitive testing not available 3, Possible - limited records but in a person with known aneurysm 4, Excluded - SAH due to other causes or other pathology
Field Note	**DO NOT CONTINUE WITH DATA ENTRY IF THE PATIENT IS EXCLUDED**
Required Field?	yes
Source	Individual patient medical records CT report Lumbar puncture report Emergency Department notes Neurosurgery review
Further description	This data will define the eligibility of the patient for inclusion into the study.

Variable / Field Name	**asah_cause**
Form Name	inclusionexclusion_criteria
Field Type	radio
Field Label	Cause of Subarachnoid Haemorrhage
Choices, Calculations	1, Cerebral Aneurysm 2, Unknown 3, Arteriovenous malformation DO NOT CONTINUE 4, Intraoperative/procedure related DO NOT CONTINUE 5, Cerebrovascular event (no subarachnoid extension) DO NOT CONTINUE 6, Extension from ICH DO NOT CONTINUE 7, Non-cerebral arteriovenous malformation DO NOT CONTINUE 8, Subarachnoid haemorrhage secondary to cancer DO NOT CONTINUE 9, Traumatic subarachnoid haemorrhage DO NOT CONTINUE 10, Non-cerebral event DO NOT CONTINUE
Field Note	Final decision of causative factors
Required Field?	yes
Source	CT report Lumbar puncture report Emergency Department notes Neurosurgery review Discharge summary
Further description	This data will define the eligibility of the patient for inclusion into the study.

Variable / Field Name	**tas**
Form Name	inclusionexclusion_criteria
Field Type	Yesno
Field Label	Does the patient live in Tasmania? (Tasmanian data only)

Field Note	**DO NOT CONTINUE WITH DATA ENTRY IF THE PATIENT DOES NOT LIVE IN TASMANIA**
Required Field?	Yes
Source	Individual patient medical record
Further description	Check residential address to confirm the patient is from Tasmania. Patients who live outside the state will be excluded from the study. Do not continue with data entry.

Variable / Field Name	**asah_hx**
Form Name	inclusionexclusion_criteria
Field Type	Dropdown
Field Label	Previous history of aSAH
Choices, Calculation	1, Yes 2, No 3, Unknown
Field Note	If yes, **Do Not Continue**
Required Field?	Yes
Source	CT reports Lumbar puncture reports Emergency Department notes Neurosurgery review Discharge summary
Further description	Patients who have had a previous aneurysmal subarachnoid haemorrhage are excluded from the study.

Variable / Field Name	**details_asah_hx**
Form Name	inclusionexclusion_criteria
Field Type	Notes
Field Label	Details of previous aSAH
Field Note	If applicable
Required Field?	No
Source	CT reports Lumbar puncture reports Emergency Department notes Neurosurgery review Discharge summary
Further description	This is a free text box. Enter a description of any previous subarachnoid haemorrhage to validate exclusion from the study.

Medical History

Medical history data are collected to help verify the inclusion and exclusion criteria and describe the study population.

Variable / Field Name	**family_history_hx**
Form Name	medical_history
Field Type	Dropdown
Field Label	Family history of aSAH?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical record; history can be obtained from participant/ subject, family member or friend.
Further description	If there is no mention of a family history of aSAH select 'unknown'. Family history data are collected to determine if subarachnoid haemorrhage (SAH) or other related diseases/disorders run in the participant's/ subject's immediate family.

Variable / Field Name	**hx_aneurysms**
Form Name	medical_history
Field Type	Dropdown
Field Label	Family history of brain aneurysms?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical records; medical history
Further description	If there is no mention of a family history of aSAH select 'unknown'. Is there a family history of brain aneurysms? Raptured and unruptured to be recorded as 'yes'

Variable / Field Name	**ruptured_aneurysm**
Form Name	medical_history
Field Type	Radio
Field Label	Does the patient have an unruptured brain aneurysm in addition to the ruptured aneurysm?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	CT reports Lumbar puncture reports Emergency Department notes Neurosurgery review Discharge summary

Variable / Field Name	**cardiovascular_hx**
Form Name	medical_history
Field Type	Dropdown
Field Label	History of Coronary Artery Disease?

Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Field Note	Acute Myocardial Infarction and/or angina =yes
Required Field?	Yes
Source	Medical records; medical history
Further description	Acute Myocardial Infarction and/or angina =yes

Variable / Field Name	**pkd_hx**
Form Name	medical_history
Field Type	Dropdown
Field Label	History of Polycystic Kidney Disease?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical records; medical history
Further description	

Variable / Field Name	**hypertension_hx**
Form Name	medical_history
Field Type	Dropdown
Field Label	History of Hypertension?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Field Note	In adults, hypertension is defined as a systolic pressure = 140 and a diastolic pressure = 90. (NINDS)
Required Field?	Yes
Source	Medical records; medical history
Further description	In adults, hypertension is defined as a systolic pressure = 140 and a diastolic pressure = 90. (NINDS)

Variable / Field Name	**hypercholesterolemia_hx**
Form Name	medical_history
Field Type	Dropdown
Field Label	History of Hypercholesterolemia?
Choices, Calculations, OR Slider Labels	1, yes 2, no 3, unknown
Required Field?	Yes
Source	Medical records; medical history
Further description	If there is no written record of Hypercholesterolemia please select not recorded.

Variable / Field Name	**Statin**
Form Name	medical_history
Field Type	Dropdown
Field Label	Hypercholesterolemia treatment at admission?
Choices, Calculations, OR Slider Labels	1, Diet 2, Statin 4, Other
Field Note	
Branching Logic (Show field only if...)	[hypercholesterolemia_hx] = '1'

Required Field?	Yes
Source	Medical records; medical history
Further description	Select the option that best describes the patient's treatment for hypercholesterolemia. Some common statins include: atorvastatin (Lipitor), fluvastatin (Lescol, Lescol XL), lovastatin (Mevacor, Altoprev), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor), and. pitavastatin (Livalo).

Variable / Field Name	**Anticoagulants**
Form Name	medical_history
Field Type	Dropdown
Field Label	Anticoagulant treatment at admission?
Choices, Calculations, OR Slider Labels	1, No 2, Aspirin 3, Clopidogrel 4, Asasantin 5, Warfarin 6, Dabigatran (Pradaxa) 7, Rivaroxaban (Xarelto) 8, Apixaban (Eliquis) 9, other
Required Field?	Yes
Source	Medical records; medical history
Further description	Select 'other' if prescribed anti-coagulant is not listed.

Variable / Field Name	**hrt_use**
Form Name	medical_history
Field Type	Dropdown
Field Label	Use of Hormone Replacement Therapy (HRT) at admission? (current use)
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Field Note	Record current use only.
Required Field?	Yes
Source	Medical records; medical history
Further description	Hormone Replacement therapy is commonly listed as HRT in the medical history. Record current use only.

Variable / Field Name	**Smoke**
Form Name	medical_history
Field Type	Dropdown
Field Label	Smoking status
Choices, Calculations, OR Slider Labels	1, Current smoker 2, Ex-smoker 3, Non-smoker 4, Unknown
Field Note	
Required Field?	Yes
Source	Medical records; medical history. History can be obtained from participant/ subject, family member or friend.

Further description	Smoking encompasses all tobacco use e.g cigarettes, e-cigarettes, pipes and cigars.

Variable / Field Name	**Alc**
Form Name	medical_history
Field Type	Dropdown
Field Label	Alcohol Intake
Choices, Calculations, OR Slider Labels	1, Never drink alcohol 2, <=4 standard drinks per week/social drinker 3, >4 standard drinks per week/Heavy drinker 4, Ex-heavy drinker 5, Unknown
Required Field?	Yes
Source	Medical record; history can be obtained from participant/ subject, family member or friend. Select 'unknown' if no information is available.
Further description	

Charlson Comorbidity Index

Variable / Field Name	**aids1**
Form Name	charlson_comorbidity_index
Field Type	Yesno
Field Label	Aids/HIV positive?
Required Field?	Yes

Variable / Field Name	**diabeties_hx_2**
Form Name	charlson_comorbidity_index
Field Type	Dropdown
Field Label	Diabetes Mellitus?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**diab_tx**
Form Name	charlson_comorbidity_index
Field Type	Dropdown
Field Label	Diabetes Mellitus treatment?
Choices, Calculations, OR Slider Labels	1, Diet 2, Insulin 3, Oral
Branching Logic (Show field only if...)	[diabeties_hx_2] = '1'
Required Field?	Yes

Variable / Field Name	**Myoinfac**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Myocardial infarction?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**Chf**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Congestive Heart Failure?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**pvd_hx**
Form Name	charlson_comorbidity_index
Field Type	Dropdown
Field Label	Peripheral vascular disease?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**Ckd**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Moderate to Severe Chronic Kidney Disease?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes
Source	
Further description	As defined by Kidney Health Australia: Kidney.org.au

Variable / Field Name	**cancer_type**
Form Name	charlson_comorbidity_index
Field Type	Dropdown
Field Label	Cancer?
Choices, Calculations, OR Slider Labels	1, Localised solid tumour 3, Leukaemia lymphoma or metastatic solid tumour 2, None
Required Field?	Yes

Variable / Field Name	**liver_d**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Liver Disease?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**Copd**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Chronic Obstructive Pulmonary Disease?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**stroke_tia**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Stroke or TIA?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Not recorded
Required Field?	Yes

Variable / Field Name	**Ctd**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Connective Tissue Disease?
Choices, Calculations, OR Slider Labels	1, Yes

	2, No
	3, Not recorded
Required Field?	Yes

Variable / Field Name	**Hemi**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Hemiplegia prior to admission for aSAH?
Choices, Calculations, OR Slider Labels	1, Yes
	2, No
	3, Not recorded
Required Field?	Yes

Variable / Field Name	**Dementia**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Dementia?
Choices, Calculations, OR Slider Labels	1, Yes
	2, No
	3, Not recorded
Required Field?	Yes

Variable / Field Name	**Pud**
Form Name	charlson_comorbidity_index
Field Type	Radio
Field Label	Peptic Ulcer Disease?
Choices, Calculations, OR Slider Labels	1, Yes
	2, No
	3, Not recorded
Required Field?	Yes

Aneurysmal Subarachnoid Haemorrhage event

Variable / Field Name	**date_event**
Form Name	asah_event
Field Type	Text
Field Label	Date of first aSAH symptom
Text Validation Type OR Show Slider Number	date_dmy
Required Field?	Yes
Source	Individual patient medical record – Nursing notes and medical notes or ambulance report.
Further description	Date of the symptom onset. This is known as the date the person was last seen, or known to be, well. (i.e., if the patient awoke with symptoms of aSAH the onset date is designated as the last time the patient was seen, or known to be, well).

Variable / Field Name	**onset_time**
Form Name	asah_event
Field Type	Text
Field Label	Time of first aSAH symptom
Text Validation Type	Time
Required Field?	Yes
Source	Individual patient medical record - Nursing notes and Medical notes, allied health records or ambulance report.
Further description	Time of the onset of aSAH symptoms, this is also known as the time the person was last seen, or known to be, well (i.e., if the patient awoke with symptoms the onset time is designated as the last time the patient was seen, or known to be well. Onset time is recorded to the nearst minute; however, time to within 15 minutes of exact time is acceptable to be coded as. If there are conflicting onset times, please use the following hierarchy: 1. stroke team/neurologist 2. admitting physician 3. emergency department physician 4. ED nursing notes 5. Emergency medical staff/Ambulance reports If onset time is unclear, then time last seen well should be recorded. In this circumstance enter the time the patient was last seen well. If approximate time last seen well is unclear, select an approximate time from the list below: Middle of the night 03:00 Breakfast 08:00 E Early morning 08:00 Morning 09:00 Late morning 10:00 Lunch 12:00 Midday or 12 Noon 12:00 Early afternoon 14:00 Afternoon or mid-afternoon 15:00 Late afternoon 16:00 Dinner/Supper 18:00 Early evening 19:00 Evening 21:00

	Late evening 22:00 Midnight 23:59 –

Variable / Field Name	**Symptoms**
Form Name	asah_event
Field Type	Checkbox
Field Label	aSAH Symptoms
Choices, Calculations	1, Headache 2, Change in level of consciousness 3, Seizure 4, Vomiting 5, Other 6, Focal Neurological deficit 7, Stiffness in neck 8, Nausea
Field Note	select all symptoms that apply
Required Field?	Yes
Source	Individual patient medical record – Emergency department notes, nursing notes and Medical notes, or ambulance report.
Further description	Select all symptoms that apply. Where there are conflicting reports, select the self-report by the patient.

Variable / Field Name	**Location**
Form Name	asah_event
Field Type	Text
Field Label	Where was the person when the aSAH event occurred?
Field Note	e.g home, work, shopping centre
Required Field?	Yes
Source	Ambulance report
Further description	Provide a brief description. Where possible use a single word only.

Variable / Field Name	**pre_residence**
Form Name	asah_event
Field Type	Dropdown
Field Label	Pre aSAH residence?
Choices, Calculations, OR Slider Labels	1, Home 2, Low level care 3, High level care
Required Field?	Yes
Source	
Further description	

Variable / Field Name	**phys_active**
Form Name	asah_event
Field Type	Dropdown
Field Label	Physical activity at symptom onset
Choices, Calculations, OR Slider Labels	1, Sedentary 2, Asleep 3, Mildly active 4, Moderately active 5, Very active 6, unknown

Required Field?	Yes
Source	
Further description	

Ambulance Times

Variable / Field Name	**ambulance_transfer**
Form Name	ambulance_times
Field Type	Radio
Field Label	Was the patient transferred to hospital by ambulance?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	yes
Further description	Arrival by ambulance refers to the patient being transported to the Emergency Department by road ambulance, air ambulance including plane and helicopter.

Variable / Field Name	**amb_date**
Form Name	ambulance_times
Field Type	Text
Field Label	Date of Ambulance transfer
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report
Further description	The date that the patient was first transported by ambulance to hospital.

Variable / Field Name	**time_amb_call**
Form Name	ambulance_times
Field Type	Text
Field Label	Time of ambulance call
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report Ambulance record
Further description	The time that the patient/carer/other called the ambulance to request assistance.

Variable / Field Name	**amb_dispatch_code**
Form Name	ambulance_times
Field Type	text
Field Label	Ambluance dispatch code
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance data – this is not available from the medical records.

Further description	What dispatch code was used? Dispatch code defines the priority of the call.

Variable / Field Name	**time_amb_arrived**
Form Name	ambulance_times
Field Type	text
Field Label	Time the ambulance arrived at the scene
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report
Further description	What time did the ambulance arrive on scene to assist the patient?

Variable / Field Name	**time_pt_loaded**
Form Name	ambulance_times
Field Type	text
Field Label	Time that the patient was loaded into the ambulance for transfer to hospital
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report
Further description	What time was the patient put into the ambulance ready for transfer to hospital?

Variable / Field Name	**arrival_1st_hosp**
Form Name	ambulance_times
Field Type	text
Field Label	Time of arrival at the first hospital
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report
Further description	What time did the ambulance arrive at the hospital? Note: this is different to the time the patient was triaged in ED. The ambulance may wait with the patient for some time at the hospital prior to triage.

Variable / Field Name	**time_triage_ed**
Form Name	ambulance_times
Field Type	text
Field Label	Time of triage in ED at the first hospital
Field Note	Time patient was triaged in ED
Text Validation Type OR Show Slider Number	time
Required Field?	Yes
Source	Ambulance report Emergency department record
Further description	What time did the ambulance arrive at the hospital? Note: this is different to the time the patient was triaged in ED. The ambulance may wait with the patient for some time at the hospital prior to triage.

Variable / Field Name	**amb_delays**
Form Name	ambulance_times
Field Type	checkbox
Field Label	Please select any documented ambulance delays
Choices, Calculations, OR Slider Labels	1, Poor access | 2, Ramped | 7, Geographical distance | 4, Secure airway | 5, Heavy lift | 6, Poor compliance | 8, other| 9, none |
Field Note	Select all that apply
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report
Further description	

Ambulance (Initial obs and tx)

Variable / Field Name	**amb_peak_int**
Form Name	ambulance_initial_obs_and_tx
Field Type	dropdown
Field Label	Ambulance: How long did the patients' headache take to reach peak intensity?
Choices, Calculations, OR Slider Labels	1, Instantaneous 2, ≤ 1min 3, ≤ 5min > 1min 4, ≤ 10min > 5min 5, ≤ 30min >10min 6, >30min 7, Unknown
Field Note	
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	
Further description	

Variable / Field Name	**amb_descrip_headach**
Form Name	ambulance_initial_obs_and_tx
Field Type	dropdown
Field Label	Ambulance: How did the patient describe their headache?
Choices, Calculations, OR Slider Labels	1, Sudden 2, Thunderclap 3, Instantaneous 4, Worst in life 5, Throbbing 6, Like a Migraine 7, Not documented 8,other
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report only
Further description	Description of headache as reported by patient. Take from ambulance reports only.

Variable / Field Name	**stroke_spec_ass**
Form Name	ambulance_initial_obs_and_tx
Field Type	radio
Field Label	Ambulance: Was a stroke-specific assessment completed?

Choices, Calculations, OR Slider Labels	1, Yes
	2, No
	3, Unknown
Field Note	e.g. FAST, ROSIER, NIHSS
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Validation: A stroke specific assessment assists in identifying stroke. Early identification may improve time to treatment.

Variable / Field Name	**time_amb_obs_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: What time were initial ambulance observations undertaken?
Field Note	time of first documented observations
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	y
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_pulse_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial pulse rate
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_systolic_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial systolic blood pressure
Field Note	First recorded systolic BP
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_diastolic_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial diastolic blood pressure
Field Note	First recorded diastolic BP
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes

Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_temp_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial temperature
Field Note	Degrees celsius
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_gcs_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial Glasgow Coma Scale (GCS)
Field Note	First recorded GCS
Text Validation Type OR Show Slider Number	number
Text Validation Min	0
Text Validation Max	15
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_bgl_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial Blood Glucose Level
Field Note	First recorded blood glucose level
Text Validation Max	Initial ambulance observations are defined as the first set of observations recorded.
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**amb_resp_rate_1**
Form Name	ambulance_initial_obs_and_tx
Field Type	text
Field Label	Ambulance: Initial respiration rate
Field Note	First recorded respiration rate
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**pupil**
Form Name	ambulance_initial_obs_and_tx
Field Type	yesno
Field Label	Pupil abnormalities (asymmetry or lack of reaction)
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	Initial ambulance observations are defined as the first set of observations recorded.

Variable / Field Name	**cpr**
Form Name	ambulance_initial_obs_and_tx
Field Type	yesno
Field Label	Was CPR required at the scene or en-route to hospital?
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	

Variable / Field Name	**intubation**
Form Name	ambulance_initial_obs_and_tx
Field Type	yesno
Field Label	Was intubation required at the scene or en-route to hospital?
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	

Variable / Field Name	**amb_aspirin**
Form Name	ambulance_initial_obs_and_tx
Field Type	radio
Field Label	Ambulance: Was Aspirin given?
Choices, Calculations, OR Slider Labels	1, Yes	2, No	3, Unknown
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	

Ambulance Final Observations

Variable / Field Name	**time_amb_obs_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: what time were final ambulance observations undertaken?
Field Note	time of discharge observations
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_pulse_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final pulse rate
Field Note	Ambulance discharge pulse rate
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_systolic_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final systolic blood pressure
Field Note	Ambulance discharge systolic BP
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_diastolic_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final diastolic blood pressure
Field Note	Ambulance discharge diastolic BP
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_temp_2**
Form Name	ambulance_final_observations

Field Type	text
Field Label	Ambulance: Final temperature
Choices, Calculations, OR Slider Labels	number
Field Note	in degrees Celsius
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_gcs_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final Glasgow Coma Scale (GCS)
Field Note	Ambulance discharge GCS
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_bgl_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final Blood Glucose Level
Field Note	Ambulance discharge blood glucose level
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_resp_rate_2**
Form Name	ambulance_final_observations
Field Type	text
Field Label	Ambulance: Final respiration rate
Field Note	Ambulance discharge respiration rate
Text Validation Type OR Show Slider Number	number
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	Yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Variable / Field Name	**amb_pt_outcome**
Form Name	ambulance_final_observations
Field Type	dropdown
Field Label	Ambulance: Patient outcome at discharge to hospital
Choices, Calculations, OR Slider Labels	1, Improved | 2, Unchanged | 3, Deteriorated | 4, Died
Branching Logic (Show field only if...)	[ambulance_transfer] = '1'
Required Field?	yes
Source	Ambulance report/data
Further description	The final observations are defined as the last set of observations prior to admission to hospital.

Hospital Arrival _1

Variable / Field Name	**hospital_name_1**
Form Name	hospital_arrival_1
Field Type	text
Field Label	Hospital Name
Required Field?	yes
Further description	The name of the first hospital at which the patient presented

Variable / Field Name	**date_hosp_arrival_1**
Form Name	hospital_arrival_1
Field Type	text
Field Label	Date of hospital arrival
Text Validation Type OR Show Slider Number	date_dmy
Required Field?	yes
Source	Admission form or patient administrative system.
Further description	The date of patient presentation to the hospital is the earliest occasion of being registered clerically or triaged

Variable / Field Name	**time_hosp_arrival_1**
Form Name	hospital_arrival_1
Field Type	text
Field Label	Time of arrival to hospital
Text Validation Type OR Show Slider Number	time
Required Field?	y
Source	Admission form or patient administrative system.
Further description	The time of patient presentation to the hospital is the earliest occasion of being registered clerically or triaged.

Variable / Field Name	**arrival_transport_1**
Form Name	hospital_arrival_1
Field Type	dropdown
Field Label	Arrival mode of transport
Choices, Calculations, OR Slider Labels	6, Ambulance with paramedic 3, Volunteer ambulance 4, Patient Transport 5, Private car/walk in 7, Fixed wing flight 8, Medical retrieval fixed wing flight 9, Medical retrieval ambulance 10, Rescue helicopter 11, Unknown
Required Field?	yes
Source	Ambulance report Emergency department notes
Further description	Select the option which best describes how the patient arrived at the hospital.

Variable / Field Name	**triage_catagory_1**
Form Name	hospital_arrival_1
Field Type	dropdown
Field Label	Triage category
Choices, Calculations, OR Slider Labels	1, Immediately life threatening 2, Imminently life threatening 3, Potentially life threatening 4, Potentially serious 5, Less urgent 6, No category noted 7, Unknown
Required Field?	No
Source	Emergency department notes
Further description	This refers to the category of priority given to the patient on arrival to the Emergency department.

Variable / Field Name	**description**
Form Name	hospital_arrival_1
Field Type	descriptive
Field Label	Emergency Department Description of Event
Required Field?	No
Source	Emergency department notes
Further description	Document the description of the aSAH event as written by the emergency department on arrival to hospital. If this is not available, leave blank. Do not substitute with another description.

Variable / Field Name	**med_contact**
Form Name	hospital_arrival_1
Field Type	radio
Field Label	Was there any medical contact within 30 days of admission (GP or hospital visit)?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	yes
Source	Emergency department notes; patient history Medical notes Allied health notes
Further description	If date of last medical contact is unknown and not within 30days, select Unknown.

Variable / Field Name	**antihypertensive_1**
Form Name	hospital_arrival_1
Field Type	yesno
Field Label	Was antihypertensive medication given in the emergency department?
Required Field?	yes
Source	Medication chart
Further description	

Variable / Field Name	**antihypertensive_date**
Form Name	hospital_arrival_1
Field Type	text

Field Label	Date of the first dose of antihypertensive in the emergency department.
Branching Logic (Show field only if...)	[antihypertensive_1] = '1'
Required Field?	y
Source	Emergency department records
Further description	This refers to the previous point 'Was antihypertensive medication given in the emergency department?'

Variable / Field Name	**antihypertensive_time_1**
Form Name	hospital_arrival_1
Field Type	text
Field Label	Time of the first dose of antihypertensive in the emergency department
Branching Logic (Show field only if...)	[antihypertensive_1] = '1'
Required Field?	yes
Source	Emergency department records
Further description	This refers to the previous point 'Was antihypertensive medication given in the emergency department?'

Variable / Field Name	**pt_admitted**
Form Name	hospital_arrival_1
Field Type	radio
Field Label	Was the patient admitted to this hospital or transferred to another hospital?
Choices, Calculations, OR Slider Labels	1, yes, the patient was admitted to this hospital 2, no, the patient was transferred to another hospital 3, no, the patient died or was sent home
Required Field?	yes
Source	Emergency department notes
Further description	Where did the patient go after the emergency department of this hospital? Patient may be transferred to another hospital for treatment.

Variable / Field Name	**transfer_reason**
Form Name	hospital_arrival_1
Field Type	notes
Field Label	What was the reason for transfer? Write a brief description.
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department notes
Further description	Write a short description of the reason for transfer. One or two sentences.

Hospital observations_1

Variable / Field Name	hosp_init_obs_1
Form Name	hospital_observations_1
Field Type	text
Field Label	What time were initial hospital observations undertaken?
Field Note	The first set of observations taken at hospital
Text Validation Type OR Show Slider Number	time
Required Field?	yes
Source	Emergency department record
Further description	The first set of observations is defined as the first set of observations taken (from arrival) at hospital. This would typically be completed in the emergency department unless the patient was taken straight to another location (e.g. ward/surgery)

Variable / Field Name	pulse_1
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial pulse rate
Text Validation Type OR Show Slider Number	number
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	systolic_1
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial systolic blood pressure
Text Validation Type OR Show Slider Number	number
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	diastolic_1
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial Diastolic blood pressure
Text Validation Type OR Show Slider Number	number
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	temp_1
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial temperature
Field Note	in degrees celsius
Text Validation Type OR Show Slider Number	number
Required Field?	Yes

Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	**gcs_1**
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial Glasgow Coma Scale (GCS)
Text Validation Type OR Show Slider Number	number
Text Validation Min	0
Text Validation Max	15
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	**bgl_1**
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial blood glucose Level
Field Note	Ambulance discharge blood glucose level
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	**resp_rate_1**
Form Name	hospital_observations_1
Field Type	text
Field Label	Initial respiration rate
Text Validation Type OR Show Slider Number	number
Required Field?	Yes
Source	Emergency department record
Further description	The first set of observations taken (from arrival) at hospital

Variable / Field Name	**wfns**
Form Name	hospital_observations_1
Field Type	radio
Field Label	World Federation of Neurosurgeons Scale (WFNS)
Choices, Calculations, OR Slider Labels	1, grade 1: GCS 15, no motor deficit. 2, grade 2: GCS 13-14 without deficit 3, grade 3: GCS 13-14 with focal neurological deficit 4, grade 4: GCS 7-12, with or without deficit. 5, grade 5: GCS < 7 , with or without deficit. 6, Not completed
Required Field?	Yes
Source	Emergency department record Medical notes Neurosurgery review
Further description	This is a standardised neurological assessment.

Hospital arrival_2

Variable / Field Name	**hosp_name_2**
Form Name	hospital_arrival_2
Field Type	text
Field Label	Hospital name
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	y
Further description	The name of the hospital that the patient was transferred to.

Variable / Field Name	**date_hosp_arrival_2**
Form Name	hospital_arrival_2
Field Type	text
Field Label	Date of hospital arrival
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	yes
Source	Admission form or patient administrative system.
Further description	The date of patient presentation to the hospital is the earliest occasion of being registered clerically or triaged

Variable / Field Name	**time_hosp_arrival_2**
Form Name	hospital_arrival_2
Field Type	text
Field Label	Time of arrival to hospital
Text Validation Type OR Show Slider Number	time
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	yes
Source	Admission form or patient administrative system.
Further description	The time of patient presentation to the hospital is the earliest occasion of being registered clerically or triaged.

Variable / Field Name	**arrival_transport_2**
Form Name	hospital_arrival_2
Field Type	dropdown
Field Label	Arrival mode of transport
Choices, Calculations, OR Slider Labels	6, Ambulance with paramedic 3, Volunteer ambulance 4, Patient Transport 5, Private car/walk in 7, Fixed wing flight 8, Medical retrieval fixed wing flight 9, Medical retrieval ambulance 10, Rescue helicopter 11, Unknown
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	y
Source	Ambulance report Emergency department notes

Further description	Select the option which best describes how the patient arrived at the hospital.

Variable / Field Name	**triage_catagory_2**
Form Name	hospital_arrival_2
Field Type	dropdown
Field Label	Triage category
Choices, Calculations, OR Slider Labels	1, Immediately life threatening 2, Imminently life threatening 3, Potentially life threatening 4, Potentially serious 5, Less urgent 6, No category noted 7, Unknown
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	No
Source	Emergency department notes
Further description	This refers to the category of priority given to the patient on arrival to the Emergency department.

Variable / Field Name	**antihypertensive_2**
Form Name	hospital_arrival_2
Field Type	yesno
Field Label	Was antihypertensive medication given?
Required Field?	yes
Source	Medication chart
Further description	

Variable / Field Name	**antihypertensive_date_2**
Form Name	hospital_arrival_2
Field Type	text
Field Label	Date of the first dose of antihypertensive
Branching Logic (Show field only if...)	[antihypertensive_2] = '1'
Required Field?	Y
Source	Emergency department records
Further description	This refers to the previous point 'Was antihypertensive medication given in the emergency department?'

Variable / Field Name	**antihypertensive_time_2**
Form Name	hospital_arrival_2
Field Type	Text
Field Label	Time of the first dose of antihypertensive
Branching Logic (Show field only if...)	[antihypertensive_2] = '1'
Required Field?	Yes
Source	Emergency department records
Further description	This refers to the previous point 'Was antihypertensive medication given in the emergency department?'

Hospital_Observations_2

Variable / Field Name	**date_init_obs_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	What date were initial hospital observations undertaken?
Field Note	The first set of observations taken at this hospital
Source	Emergency department record Nursing notes
Further description	The date of the first set of observations. Defined as the first set of observations taken (from arrival) at hospital. This would typically be completed in the emergency department unless the patient was taken straight to another location (e.g. ward/surgery)

Variable / Field Name	**time_init_obs_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	What time were initial hospital observations undertaken?
Field Note	The first set of observations taken at this hospital
Text Validation Type OR Show Slider Number	Time
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	The time of the first set of observations. Defined as the first set of observations taken (from arrival) at hospital. This would typically be completed in the emergency department unless the patient was taken straight to another location (e.g. ward/surgery)

Variable / Field Name	**pulse_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Pulse rate
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	Defined as the first set of observations taken (from arrival) at hospital.

Variable / Field Name	**systolic_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Systolic blood pressure
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	Defined as the first set of observations taken (from arrival) at hospital.

Variable / Field Name	**diastolic_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Diastolic blood pressure
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	Defined as the first set of observations taken (from arrival) at hospital.

Variable / Field Name	**temp_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Temperature
Field Note	in degrees Celsius
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	Defined as the first set of observations taken (from arrival) at hospital.

Variable / Field Name	**gcs_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Glasgow Coma Scale (GCS)
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Required Field?	Yes
Source	Emergency department record Nursing notes
Further description	Defined as the first set of observations taken (from arrival) at hospital.

Variable / Field Name	**bgl_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Blood glucose Level
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Source	Yes
Further description	Emergency department record Nursing notes

Variable / Field Name	**resp_rate_2**
Form Name	hospital_observations_2
Field Type	Text
Field Label	Respiration rate
Text Validation Type OR Show Slider Number	Number
Branching Logic (Show field only if...)	[pt_admitted] = '2'
Source	Yes

Further description	Emergency department record
	Nursing notes

Variable / Field Name	**wfns_2**
Form Name	hospital_observations_2
Field Type	Radio
Field Label	World Federation of Neurosurgeons Scale (WFNS)
Choices, Calculations, OR Slider Labels	1, grade 1: GCS 15, no motor deficit.
	2, grade 2: GCS 13-14 without deficit
	3, grade 3: GCS 13-14 with focal neurological deficit
	4, grade 4: GCS 7-12, with or without deficit.
	5, grade 5: GCS < 7 , with or without deficit.
	6, Not completed
Required Field?	Yes
Source	Emergency department record
	Medical notes
	Neurosurgery review
Further description	This is a standardised neurological assessment.

Diagnostic imaging

Variable / Field Name	**pt_ct**
Form Name	diagnostic_imaging
Field Type	Radio
Field Label	Did the patient have a CT scan prior to treatment?
Choices, Calculations, OR Slider Labels	1, Yes | 2, No | 3, Unknown
Required Field?	Yes
Source	Radiology report
Further description	If the patient had any type of Computed Tomography (e.g CTA, CTP, non-contrast CT) select 'yes'.

Variable / Field Name	**date_ct**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Date of the CT
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[pt_ct] = '1'
Required Field?	Yes
Source	Radiology report
Further description	If the patient had more than one CT, enter the data for the first aSAH diagnostic CT

Variable / Field Name	**time_ct**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Time of the CT
Text Validation Type OR Show Slider Number	Time
Branching Logic (Show field only if...)	[pt_ct] = '1'
Required Field?	Yes
Source	Radiology report
Further description	The time of the CT as noted on the scan itself

Variable / Field Name	**type_ct**
Form Name	diagnostic_imaging
Field Type	Checkbox
Field Label	What type of CT scan was it? Select all that apply.
Choices, Calculations, OR Slider Labels	1, Non contrast CT (plain) | 2, CT angiogram | 3, CT perfusion | 4, Unknown
Field Note	Select all that apply
Branching Logic (Show field only if...)	[pt_ct] = '1'
Required Field?	Yes
Source	Radiology report
Further description	Select the type of CT undertaken as for the scan recorded in the previous data points.

Variable / Field Name	**pt_mri**
Form Name	diagnostic_imaging
Field Type	Checkbox
Field Label	Did the patient have an MRI prior to treatment?
Choices, Calculations, OR Slider Labels	1, Yes | 2, No | 3, Unknown
Required Field?	Yes
Source	Radiology report

Further description	

Variable / Field Name	**date_mri**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Date of the MRI
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[pt_mri(1)] = '1'
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**time_mri**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Time of the MRI
Text Validation Type OR Show Slider Number	Time
Branching Logic (Show field only if...)	[pt_mri(1)] = '1'
Required Field?	Yes
Source	Radiology report
Further description	The time of the MRI as noted on the scan

Variable / Field Name	**pt_lumb**
Form Name	diagnostic_imaging
Field Type	Radio
Field Label	Did the patient have a lumbar puncture prior to treatment?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Diagnostics – sort by date
Further description	

Variable / Field Name	**date_lumb**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Date of lumbar puncture
Branching Logic (Show field only if...)	[pt_lumb] = '1'
Required Field?	Yes
Source	Diagnostics
Further description	

Variable / Field Name	**time_lumb**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Time of lumbar puncture
Branching Logic (Show field only if...)	[pt_lumb] = '1'
Required Field?	No
Source	Lumbar puncture report
Further description	

Variable / Field Name	**lumb_rbc**

Form Name	diagnostic_imaging
Field Type	Radio
Field Label	Which best describes the results of the lumbar puncture?
Choices, Calculations, OR Slider Labels	1, Unequivocally abnormal (xanthochromia, elevated red-cell count unchanged from tube 1 to tube 4) 2, Abnormal but equivocal (elevated red-cell count without xanthochromia or analysis of only 1 tube) 3, Normal
Branching Logic (Show field only if...)	[pt_lumb] = '1'
Required Field?	Yes
Source	Lumbar puncture report
Further description	

Variable / Field Name	**pt_dsa**
Form Name	diagnostic_imaging
Field Type	Radio
Field Label	Did the patient have a DSA (Digital Subtraction angiography)?
Choices, Calculations, OR Slider Labels	1, Yes | 2, No | 3, Unknown
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**date_dsa**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Date of DSA
Branching Logic (Show field only if...)	[pt_dsa] = '1'
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**time_dsa**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Time of DSA
Branching Logic (Show field only if...)	[pt_dsa] = '1'
Required Field?	No
Source	Endovascular report
Further description	Record the groin puncture time

Variable / Field Name	**multiple_aneurysms**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Multiple aneurysms?
Choices, Calculations, OR Slider Labels	1, Yes 2, No
Field Note	Is there more than one aneurysm noted on the radiology report?
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**aneurysm_ident**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Can the ruptured aneurysm be identified
Choices, Calculations, OR Slider Labels	1, Yes 2, No
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**post_ant**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Posterior or anterior?
Choices, Calculations, OR Slider Labels	1, Posterior 2, Anterior
Branching Logic (Show field only if...)	[aneurysm_ident] = '1'
Required Field?	No
Source	Radiology report
Further description	

Variable / Field Name	**aneurysm_side**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Aneurysm side?
Choices, Calculations, OR Slider Labels	1, Right 2, Left 3, Midline
Branching Logic (Show field only if...)	[aneurysm_ident] = '1'
Required Field?	No
Source	Radiology report
Further description	

Variable / Field Name	**aneurysm_loc**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Aneurysm specific location
Choices, Calculations, OR Slider Labels	1, Pcomm 2, AChoA 3, ICA terminus 4, ACA - A1 5, ACA - Acomm 6, ACA -Pericallosal/callosomarginal 7, MCA - M1 before major bif/trifurcation 8, MCA - at bifurcation/trifurcation 9, MCA - distal MCA (Distal MCA is beyond the MCA bifurcation or trifurcation) 10, PCA - distal 11, PCA - P2 12, PCA - P1 13, basilar bifurcation 14, SCA 15, Basilar trunk 16, AICA 17, Vertebral_basilar junction 18, Vertebral

Field Note	To be verified by clinician
Branching Logic (Show field only if...)	[aneurysm_ident] = '1'
Required Field?	No
Source	Radiology report
Further description	

Variable / Field Name	**fisher_scale**
Form Name	diagnostic_imaging
Field Type	Dropdown
Field Label	Modified Fisher Scale grade:
Choices, Calculations, OR Slider Labels	1, Grade 0: No SAH or IVH 2, Grade 1: SAH less than 1mm thick, no IVH 3, Grade 2: SAH less than 1mm thick, with IVH 4, Grade 3: SAH more than 1mm thick, no IVH 5, Grade 4: SAH more than 1mm thick, with IVH
Field Note	Complete if available
Required Field?	No
Source	Radiology report Neurosurgeon report
Further description	

Variable / Field Name	**aneurysm_size**
Form Name	diagnostic_imaging
Field Type	Text
Field Label	Maximum aneurysm in size (mm)
Field Note	in milimeters
Required Field?	No
Source	CTA Neurosurgeon report Endovasular report
Further description	Record the largest measurement. For example if the aneurysm is 4.4 x 2.1 x 3.0, you would record 4.4

Treatment details

Variable / Field Name	**ventriculostomy**
Form Name	treatment_details
Field Type	Yesno
Field Label	Ventriculostomy placement for hydrocephalus prior to clipping and coiling?
Required Field?	Yes
Source	Medical records Radiological reports
Further description	

Variable / Field Name	**rebleed1**
Form Name	treatment_details
Field Type	radio
Field Label	Rebleed prior to treatment?
Choices, Calculations, OR Slider Labels	1, Yes - confirmed on neuroimaging 2, Possible - acute clinical deterioration clinically suspected to be a rebleed but no radiological confirmation 3, No - no change in clinical status
Required Field?	yes
Source	Medical records Radiological reports
Further description	

Variable / Field Name	**seizure_activity**
Form Name	treatment_details
Field Type	dropdown
Field Label	Was there any seizure activity prior to coiling or clipping?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	yes
Source	Medical records
Further description	

Variable / Field Name	**coiling**
Form Name	treatment_details
Field Type	yesno
Field Label	Did the patient receive endovascular coiling?
Required Field?	yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**date_coiling**
Form Name	treatment_details
Field Type	Text
Field Label	Date of endovascular coiling
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[coiling] = '1'
Required Field?	Yes
Source	Neurosurgical records

Further description	

Variable / Field Name	**time_coiling**
Form Name	treatment_details
Field Type	Text
Field Label	Time of endovascular coiling
Branching Logic (Show field only if...)	[coiling] = '1'
Required Field?	Yes
Source	Neurosurgical records
Further description	Record the groin puncture time

Variable / Field Name	**Clipping**
Form Name	treatment_details
Field Type	Yesno
Field Label	Did the patient receive microsurgical clipping?
Field Note	Surgical start time
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**date_clipping**
Form Name	treatment_details
Field Type	text
Field Label	Date of microsurgical clipping
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[clipping] = '1'
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**time_clipping**
Form Name	treatment_details
Field Type	Text
Field Label	Time of microsurgical clipping
Field Note	surgical start time
Branching Logic (Show field only if...)	[clipping] = '1'
Required Field?	Yes
Source	Neurosurgical records
Further description	Record the surgery start time

Variable / Field Name	**treatment_result**
Form Name	treatment_details
Field Type	Dropdown
Field Label	Treatment result
Choices, Calculations, OR Slider Labels	1, Complete Occlusion 2, Neck remnant 3, Residual Fundus 4, Unsecured
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**Haematoma**
Form Name	treatment_details
Field Type	Yesno
Field Label	Haematoma evacuation?
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**no_tx**
Form Name	treatment_details
Field Type	Text
Field Label	Number of aneurysms treated?
Field Note	write unknown if not documented
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**intraoperative_rupture**
Form Name	treatment_details
Field Type	Dropdown
Field Label	Intraoperative rupture?
Choices, Calculations, OR Slider Labels	1, Yes - major: leading to intracranial pressure necessitating additional surgery, resulting in hypotension or requiring blood transfusion 2, Yes - Minor: any other rupture from any treated aneurysm 3, No 4, Unknown
Field Note	see NINDS definition
Required Field?	Yes
Source	Neurosurgical records
Further description	

Variable / Field Name	**Nimodopine**
Form Name	treatment_details
Field Type	Yesno
Field Label	Was nimodopine given
Required Field?	Yes
Source	Emergency record Day after surgery
Further description	Do not record any dose given during sugery.

Variable / Field Name	**date_nimodopine**
Form Name	treatment_details
Field Type	Text
Field Label	Date nimodopine given?
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[nimodopine] = '1'
Required Field?	Yes
Source	Medical Records
Further description	

Variable / Field Name	**time_nimodopine**
Form Name	treatment_details

Field Type	Text
Field Label	Time of the first dose of nimodopine
Text Validation Type OR Show Slider Number	Time
Branching Logic (Show field only if...)	[nimodopine] = '1'
Required Field?	Yes
Source	Medical Records
Further description	

Complications

Variable / Field Name	**Haemorrhage**
Form Name	Complications
Field Type	Yesno
Field Label	New haemorrhage or ischaemic stroke on postoperative scan performed within first 48 hours?
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**Rebleeding**
Form Name	Complications
Field Type	Dropdown
Field Label	Was there post-treatment rebleed?
Choices, Calculations, OR Slider Labels	1, Yes - confirmed on neuroimaging 2, No 3, Suspected but unconfirmed neuroimaging
Required Field?	Yes
Source	Radiology report
Further description	

Variable / Field Name	**date_of_rebleed**
Form Name	Complications
Field Type	Text
Field Label	Date of rebleed
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[rebleeding] = '1'
Required Field?	Yes
Source	Medical notes Radiology report
Further description	

Variable / Field Name	**re_treatment_required**
Form Name	Complications
Field Type	Yesno
Field Label	Aneurysm re-treatment required?
Branching Logic (Show field only if...)	[rebleeding] = '1'
Required Field?	Yes
Source	Medical records
Further description	

Variable / Field Name	**re_treatment_type**
Form Name	Complications
Field Type	Dropdown
Field Label	Aneurysm re-treatment type?
Choices, Calculations, OR Slider Labels	1, Surgery | 2, Endovascular
Branching Logic (Show field only if...)	[re_treatment_required] = '1'
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**haem_evac**

Form Name	Complications
Field Type	Yesno
Field Label	Was there emergency evacuation of the haematoma?
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**del_cerebral_inj**
Form Name	Complications
Field Type	Radio
Field Label	Confirmed delayed cerebral injury?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Field Note	As per NINDS definition - DCI is defined as the presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**endo_cereb_isch**
Form Name	Complications
Field Type	Dropdown
Field Label	Did the patient receive endovascular therapy for delayed cerebral ischemia?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**clinical_deterioration**
Form Name	Complications
Field Type	Dropdown
Field Label	Did the patient experience clinical deterioration due to delayed cerebral ischaemia?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Field Note	NINDS definition - The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**endovasc_ther_received**
Form Name	Complications
Field Type	Dropdown
Field Label	Endovascular therapy received
Choices, Calculations, OR Slider Labels	1, Endovascular balloon angioplasty 2, Endovascular vasodilator therapy
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**endovasc_tx_no**
Form Name	Complications
Field Type	Text
Field Label	How many endovascular therapy treatments did they receive?
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**post_treatment_infec**
Form Name	Complications
Field Type	Dropdown
Field Label	Post-treatment infection
Choices, Calculations, OR Slider Labels	1, No 2, Yes - meningitis/ventriculitis 3, Yes - pneumonia 4, Yes - line related 5, Yes - UTI 6, Yes – other
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**post_treatment_seizure**
Form Name	Complications
Field Type	Dropdown
Field Label	In Hospital post-treatment seizure?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical notes
Further description	

Variable / Field Name	**ventriculo_placement**
Form Name	Complications
Field Type	Dropdown
Field Label	Ventriculostomy placement after treatment?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical notes

Further description	

Variable / Field Name	**shunt_placement**
Form Name	Complications
Field Type	Dropdown
Field Label	Shunt placement in hospital after treatment?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical notes Discharge summary
Further description	

Variable / Field Name	**icu2**
Form Name	Complications
Field Type	Yesno
Field Label	ICU admission required
Required Field?	Yes
Source	Medical record
Further description	Was the patient admitted to ICU?

Variable / Field Name	**comfort_measures_only**
Form Name	Complications
Field Type	Dropdown
Field Label	Was care restricted to 'comfort measures only'?
Choices, Calculations, OR Slider Labels	1, Yes 2, No 3, Unknown
Required Field?	Yes
Source	Medical notes Admission/discharge records
Further description	

Variable / Field Name	**comfort_care_start**
Form Name	Complications
Field Type	Text
Field Label	If care was 'comfort measures' only, what date did this care type start?
Text Validation Type OR Show Slider Number	date_dmy
Branching Logic (Show field only if...)	[comfort_measures_only] = '1'
Required Field?	No
Source	
Further description	

Discharge

Variable / Field Name	**discharge_destination**
Form Name	Discharge
Field Type	Radio
Field Label	Where was the patient discharged to following their acute hospital admission?
Choices, Calculations, OR Slider Labels	1, Home 2, Rehabilitation 3, Another hospital 4, Nursing home 5, Died
Required Field?	Y
Source	
Further description	

Variable / Field Name	**death_hosp**
Form Name	Discharge
Field Type	Dropdown
Field Label	Cause of death in hospital
Choices, Calculations, OR Slider Labels	1, Initial bleeding 2, Rebleeding 3, Delayed cerebral ischemia 4, Cardiac 5, Respiratory 6, Sepsis 7, other
Field Note	As per death certificate
Required Field?	
Source	
Further description	

Variable / Field Name	**dischrg_mobility**
Form Name	Discharge
Field Type	Notes
Field Label	Was a physiotherapy assessment completed at discharge? Describe the patient's mobility.
Required Field?	
Source	
Further description	

Variable / Field Name	**Fim**
Form Name	Discharge
Field Type	Text
Field Label	Functional Independence Measure Score (FIM) at admission to rehabilitation.
Field Note	recorded at discharge from hospital
Required Field?	
Source	
Further description	

Variable / Field Name	**fim_2**
Form Name	Discharge
Field Type	Text
Field Label	Functional Independence Measure Score (FIM) at discharge from rehabilitation

Field Note	recorded at discharge from hospital
Required Field?	
Source	
Further description	

Bibliography:

1.   Martin CO, Rymer MM. Hemorrhagic stroke: Aneurysmal subarachnoid hemorrhage. *Missouri medicine*. 2011;108:124

2.   Grasso G, Alafaci C, Macdonald RL. Management of aneurysmal subarachnoid hemorrhage: State of the art and future perspectives. *Surg Neurol Int*. 2017;8:11-11

3.   Kakarieka A. Review on traumatic subarachnoid hemorrhage. *Neurological research*. 1997;19:230-232

4.   Rinkel G, van Gijn J, Wijdicks E. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. *Stroke*. 1993;24:1403-1409

5.   Luoma A, Reddy U. Acute management of aneurysmal subarachnoid haemorrhage. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2013;13:52-58

6.   Barboza MA, Maud A, Rodriguez GJ. Reversible cerebral vasoconstriction syndrome and nonaneurysmal subarachnoid hemorrhage. *Journal of vascular and interventional neurology*. 2014;7:17

7.   Calviere L, Viguier A, Patsoura S, Rousseau V, Albucher J-F, Planton M, et al. Risk of intracerebral hemorrhage and mortality after convexity subarachnoid hemorrhage in cerebral amyloid angiopathy. *Stroke*. 2019;50:2562-2564

8.   Edjlali M, Rodriguez-Régent C, Hodel J, Aboukais R, Trystram D, Pruvo J-P, et al. Subarachnoid hemorrhage in ten questions. *Diagnostic and interventional imaging*. 2015;96:657-666

9.   Cheng Y-C, Kuo K-H, Lai T-H. A common cause of sudden and thunderclap headaches: Reversible cerebral vasoconstriction syndrome. *The journal of headache and pain*. 2014;15:13

10.   Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *New England Journal of Medicine*. 2000;342:29-36

11.   Pereira JLB, de Albuquerque LAF, Dellaretti M, de Carvalho GTC, Junior GV, Rocha MI, et al. Importance of recognizing sentinel headache. *Surg Neurol Int*. 2012;3

12.   Keedy A. An overview of intracranial aneurysms. *McGill Journal of Medicine: MJM*. 2006;9:141

13.   Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2016;87:1118-1123

14.   Korja M, Kaprio J. Controversies in epidemiology of intracranial aneurysms and sah. *Nature Reviews Neurology*. 2016;12:50

15.   Huang J, Van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: A meta-analysis. *Neurosurgery*. 2002;51:1101-1107

16. Ridwan S, Urbach H, Greschus S, von Hagen J, Esche J, Boström A. Health care costs of spontaneous aneurysmal subarachnoid hemorrhage for rehabilitation, home care, and in-hospital treatment for the first year. *World neurosurgery*. 2017;97:495-500

17. Petridis AK, Kamp MA, Cornelius JF, Beez T, Beseoglu K, Turowski B, et al. Aneurysmal subarachnoid hemorrhage: Diagnosis and treatment. *Deutsches Ärzteblatt International*. 2017;114:226

18. Linn F, Rinkel G, Algra A, Van Gijn J. Incidence of subarachnoid hemorrhage: Role of region, year, and rate of computed tomography: A meta-analysis. *Stroke*. 1996;27:625-629

19. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: A systematic review with emphasis on region, age, gender and time trends. *Journal of Neurology, Neurosurgery & Psychiatry*. 2007;78:1365-1372

20. Hughes JD, Bond KM, Mekary RA, Dewan MC, Rattani A, Baticulon R, et al. Estimating the global incidence of aneurysmal subarachnoid hemorrhage: A systematic review for central nervous system vascular lesions and meta-analysis of ruptured aneurysms. *World neurosurgery*. 2018;115:430-447. e437

21. Etminan N, Chang H-S, Hackenberg K, De Rooij NK, Vergouwen MD, Rinkel GJ, et al. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: A systematic review and meta-analysis. *JAMA neurology*. 2019;76:588-597

22. van Lieshout JH, Dibué-Adjei M, Cornelius JF, Slotty PJ, Schneider T, Restin T, et al. An introduction to the pathophysiology of aneurysmal subarachnoid hemorrhage. *Neurosurgical review*. 2018;41:917-930

23. Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new noncraniotomy model of subarachnoid hemorrhage in the rat. *Stroke*. 1995;26:1086-1092

24. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: Proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391-2395

25. Van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *The Lancet*. 2007;369:306-318

26. Peters SA, Norton R. Sex and gender reporting in global health: New editorial policies. 2018

27. Bushnell C, Howard VJ, Lisabeth L, Caso V, Gall S, Kleindorfer D, et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. *The Lancet Neurology*. 2018;17:641-650

28. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2014;45:1545-1588

29. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from the american heart association. *Journal of the American College of Cardiology*. 2011;57:1404-1423

30. Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: A systematic analysis of the global burden of disease study 2017. *Neuroepidemiology*. 2020;54:171-179

31. Ikawa F, Hidaka T, Yoshiyama M, Ohba H, Matsuda S, Ozono I, et al. Characteristics of cerebral aneurysms in japan. *Neurologia medico-chirurgica*. 2019:ra. 2019-0099

32. van Munster CE, von und zu Fraunberg M, Rinkel GJ, Rinne J, Koivisto T, Ronkainen A. Differences in aneurysm and patient characteristics between cohorts of finnish and dutch patients with subarachnoid hemorrhage: Time trends between 1986 and 2005. *Stroke*. 2008;39:3166-3171

33. Kristensen MØ. Increased incidence of bleeding intracranial aneurysms in greenlandic eskimos. *Acta neurochirurgica*. 1983;67:37-43

34. Australian bureau of statistics. Https://www.Abs.Gov.Au/statistics/health/health-conditions-and-risks/national-health-survey-first-results/latest-release. Accessed november 20, 2020.

35. Anderson CS, Chakera TMH, Stewart-Wynne EQ, Jamrozik KD, Burvill PW, Johnson GA. Determining the incidence of different subtypes of stroke: Results from the perth community stroke study, 1989–1990. *Medical Journal of Australia*. 1993;158:85-89

36. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in perth, western australia. *Stroke*. 1999;30:2105-2111

37. Islam MS, Anderson CS, Hankey GJ, Hardie K, Carter K, Broadhurst R, et al. Trends in incidence and outcome of stroke in perth, western australia during 1989 to 2001: The perth community stroke study. *Stroke*. 2008;39:776-782

38. Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes: Initial findings from the north east melbourne stroke incidence study (nemesis). *Stroke*. 2001;32:1732-1738

39. Thrift AG, Dewey HM, Sturm JW, Srikanth VK, Gilligan AK, Gall SL, et al. Incidence of stroke subtypes in the north east melbourne stroke incidence study (nemesis): Differences between men and women. *Neuroepidemiology*. 2009;32:11-18

40.   Hankey G, Jamrozik K, Broadhurst R. Epidemiology of aneurysmal subarachnoid hemorrhage in australia and new zealand-incidence and case fatality from the australasian cooperative research on subarachnoid hemorrhage study (across). *Stroke*. 2000;31:1843-1850

41.   Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study. *Stroke*. 2013;44:1226-1231

42.   Newbury J, Kleinig T, Leyden J, Arima H, Castle S, Cranefield J, et al. Stroke epidemiology in an australian rural cohort (search). *International Journal of Stroke*. 2017;12:161-168

43.   Nichols L, Stirling C, Otahal P, Stankovich J, Gall S. Socioeconomic disadvantage is associated with a higher incidence of aneurysmal subarachnoid hemorrhage. *Journal of stroke and cerebrovascular diseases*. 2018;27:660-668

44.   Thompson BG, Brown Jr RD, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly Jr ES, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2015;46:2368-2400

45.   Toth G, Cerejo R. Intracranial aneurysms: Review of current science and management. *Vascular Medicine*. 2018;23:276-288

46.   Harada K, Fukuyama K, Shirouzu T, Ichinose M, Fujimura H, Kakumoto K, et al. Prevalence of unruptured intracranial aneurysms in healthy asymptomatic japanese adults: Differences in gender and age. *Acta neurochirurgica*. 2013;155:2037-2043

47.   Ziemba-Davis M, Bohnstedt BN, Payner TD, Leipzig TJ, Palmer E, Cohen-Gadol AA. Incidence, epidemiology, and treatment of aneurysmal subarachnoid hemorrhage in 12 midwest communities. *Journal of Stroke and Cerebrovascular Diseases*. 2014;23:1073-1082

48.   Teunissen LL, Rinkel GJ, Algra A, Van Gijn J. Risk factors for subarachnoid hemorrhage: A systematic review. *Stroke*. 1996;27:544-549

49.   Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: An updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773-2780

50.   Ghods AJ, Lopes D, Chen M. Gender differences in cerebral aneurysm location. *Frontiers in neurology*. 2012;3:78

51.   Horiuchi T, Tanaka Y, Hongo K. Sex-related differences in patients treated surgically for aneurysmal subarachnoid hemorrhage. *Neurologia medico-chirurgica*. 2006;46:328-332

52.   Hamdan A, Barnes J, Mitchell P. Subarachnoid hemorrhage and the female sex: Analysis of risk factors, aneurysm characteristics, and outcomes. *Journal of neurosurgery*. 2014;121:1367-1373

53. Wang G-X, Zhang D, Wang Z-P, Yang L-Q, Yang H, Li W. Risk factors for ruptured intracranial aneurysms. *The Indian journal of medical research*. 2018;147:51

54. World health organization.International classification of functioning, disability and health (icf). Https://www.Who.Int/classifications/international-classification-of-functioning-disability-and-health. Accessed on nov 22, 2020.

55. Classification of functioning, disability and health (icf). Https://sustainable-design.Ie/arch/icidh-2final.Pdfinternational. Accessed on nov 21, 2020.

56. Sulter G, Steen C, Keyser JD. Use of the barthel index and modified rankin scale in acute stroke trials. *Stroke*. 1999;30:1538-1541

57. Oczkowski WJ, Barreca S. The functional independence measure: Its use to identify rehabilitation needs in stroke survivors. *Archives of Physical Medicine and Rehabilitation*. 1993;74:1291-1294

58. Broderick JP, Adeoye O, Elm J. Evolution of the modified rankin scale and its use in future stroke trials. *Stroke*. 2017;48:2007-2012

59. Centers for disease control and prevention. Https://www.Cdc.Gov/hrqol/index.Htm. Accessed on nov 21, 2020.

60. Gil-Lacruz M, Gil-Lacruz AI, Gracia-Pérez ML. Health-related quality of life in young people: The importance of education. *Health and quality of life outcomes*. 2020;18:1-13

61. Gusi N, Olivares P, Rajendram R. The eq-5d health-related quality of life questionnaire. *Handbook of disease burdens and quality of life measures. New York: Springer*. 2010:87-99

62. Lins L, Carvalho FM. Sf-36 total score as a single measure of health-related quality of life: Scoping review. *SAGE open medicine*. 2016;4:2050312116671725

63. Cech DJ, Martin ST. Chapter 5 - evaluation of function, activity, and participation. In: Cech DJ, Martin ST, eds. *Functional movement development across the life span (third edition)*. Saint Louis: W.B. Saunders; 2012:88-104.

64. Kongable GL, Lanzino G, Germanson TP, Truskowski LL, Alves WM, Torner JC, et al. Gender-related differences in aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 1996;84:43-48

65. De Marchis GM, Schaad C, Fung C, Beck J, Gralla J, Takala J, et al. Gender-related differences in aneurysmal subarachnoid hemorrhage: A hospital based study. *Clinical Neurology and Neurosurgery*. 2017;157:82-87

66. Nieuwkamp DJ, Vaartjes I, Algra A, Bots ML, Rinkel GJ. Age-and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the netherlands. *International Journal of Stroke*. 2013;8:90-94

67. Stienen MN, Burkhardt J, Neidert M, Fung C, Bervini D, Zumofen D, et al. Predictors of in-hospital death following aneurysmal subarachnoid hemorrhage–analysis of a

nationwide database (swiss sos). *Journal of Neurological Surgery Part A: Central European Neurosurgery*. 2017;78:O11

68.   Koffijberg H, Buskens E, Granath F, Adami J, Ekbom A, Rinkel G, et al. Subarachnoid haemorrhage in sweden 1987–2002: Regional incidence and case fatality rates. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008;79:294-299

69.   Duijghuisen JJ, Greebe P, Nieuwkamp DJ, Algra A, Rinkel GJ. Sex-related differences in outcome in patients with aneurysmal subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*. 2016;25:2067-2070

70.   Pobereskin L. Incidence and outcome of subarachnoid haemorrhage: A retrospective population based study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2001;70:340-343

71.   Schertz M, Mehdaoui H, Hamlat A, Piotin M, Banydeen R, Mejdoubi M. Incidence and mortality of spontaneous subarachnoid hemorrhage in martinique. *PloS one*. 2016;11

72.   Macpherson KJ, Lewsey JD, Jhund PS, Gillies M, Chalmers JW, Redpath A, et al. Trends in incidence and in short term survival following a subarachnoid haemorrhage in scotland, 1986-2005: A retrospective cohort study. *BMC neurology*. 2011;11:38

73.   Sheikh K, Bullock CM. Effect of measurement on sex difference in stroke mortality. *Stroke*. 2007;38:1085-1087

74.   Vaartjes I, Reitsma J, Berger-van Sijl M, Bots M. Gender differences in mortality after hospital admission for stroke. *Cerebrovascular diseases*. 2009;28:564-571

75.   Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the international subarachnoid aneurysm trial (isat): Long-term follow-up. *The Lancet Neurology*. 2009;8:427-433

76.   Ronkainen A, Niskanen M, Rinne J, Koivisto T, Hernesniemi J, Vapalahti M. Evidence for excess long-term mortality after treated subarachnoid hemorrhage. *Stroke*. 2001;32:2850-2853

77.   Wik KE, Lindegaard KF, Brunborg B, Bjørk IT, Ruland C. [life following acute subarachnoid haemorrhage]. *Tidsskr Nor Laegeforen*. 2005;125:152-154

78.   Tjahjadi M, Heinen C, König R, Rickels E, Wirtz CR, Woischneck D, et al. Health-related quality of life after spontaneous subarachnoid hemorrhage measured in a recent patient population. *World neurosurgery*. 2013;79:296-307

79.   Hammer A, Steiner A, Ranaie G, Yakubov E, Erbguth F, Hammer CM, et al. Impact of comorbidities and smoking on the outcome in aneurysmal subarachnoid hemorrhage. *Scientific reports*. 2018;8:1-7

80.   Duan C, Zheng K, Zhong M, Zhao B, Chen YS, Tan XX, et al. Poor-grade aneurysmal subarachnoid hemorrhage: Risk factors affecting clinical outcomes in

intracranial aneurysm patients in a multi-center study. *Frontiers in Neurology*. 2019;10:123

81.   Ronne-Engström E, Enblad P, Lundström E. Health-related quality of life at median 12 months after aneurysmal subarachnoid hemorrhage, measured with euroqol-5d. *Acta neurochirurgica*. 2013;155:587-593

82.   Wermer M, Greebe P, Algra A, Rinkel GJ. Long-term mortality and vascular event risk after aneurysmal subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery & Psychiatry*. 2009;80:1399-1401

83.   Huttunen T, von und zu Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Sankila R, et al. Long-term excess mortality of 244 familial and 1502 sporadic one-year survivors of aneurysmal subarachnoid hemorrhage compared with a matched eastern finnish catchment population. *Neurosurgery*. 2011;68:20-27

84.   Huhtakangas J, Lehto H, Seppä K, Kivisaari R, Niemelä M, Hernesniemi J, et al. Long-term excess mortality after aneurysmal subarachnoid hemorrhage: Patients with multiple aneurysms at risk. *Stroke*. 2015;46:1813-1818

85.   Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:2315-2321

86.   Galea JP, Dulhanty L, Patel HC. Predictors of outcome in aneurysmal subarachnoid hemorrhage patients: Observations from a multicenter data set. *Stroke*. 2017;48:2958-2963

87.   Lanzino G, Kassell NF, Germanson TP, Kongable GL, Truskowski LL, Torner JC, et al. Age and outcome after aneurysmal subarachnoid hemorrhage: Why do older patients fare worse? *Journal of neurosurgery*. 1996;85:410-418

88.   Germans MR, Jaja BN, de Oliviera Manoel AL, Cohen AH, Macdonald RL. Sex differences in delayed cerebral ischemia after subarachnoid hemorrhage. *Journal of neurosurgery*. 2017;129:458-464

89.   Rodríguez DR, Matamoros CS, Cúe LF, Hernández JM, Sánchez YP, Nellar JP. Factors associated with poor outcome for aneurysmal subarachnoid haemorrhage in a series of 334 patients. *Neurología (English Edition)*. 2017;32:15-21

90.   De Marchis GM, Lantigua H, Schmidt JM, Lord AS, Velander AJ, Fernandez A, et al. Impact of premorbid hypertension on haemorrhage severity and aneurysm rebleeding risk after subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014;85:56-59

91.   Jaja BN, Lingsma H, Schweizer TA, Thorpe KE, Steyerberg EW, Macdonald RL. Prognostic value of premorbid hypertension and neurological status in aneurysmal subarachnoid hemorrhage: Pooled analyses of individual patient data in the sahit repository. *Journal of neurosurgery*. 2015;122:644-652

92. Ayling OG, Ibrahim GM, Alotaibi NM, Gooderham PA, Macdonald RL. Dissociation of early and delayed cerebral infarction after aneurysmal subarachnoid hemorrhage. *Stroke*. 2016;47:2945-2951

93. D'Souza S. Aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgical Anesthesiology*. 2015;27

94. Lindekleiv H, Sandvei MS, Njolstad I, Lochen ML, Romundstad PR, Vatten L, et al. Sex differences in risk factors for aneurysmal subarachnoid hemorrhage: A cohort study. *Neurology*. 2011;76:637-643

95. Koshy L, Easwer HV, Premkumar S, Alapatt JP, Pillai AM, Nair S, et al. Risk factors for aneurysmal subarachnoid hemorrhage in an indian population. *Cerebrovascular diseases (Basel, Switzerland)*. 2010;29:268-274

96. Weir BK, Kongable GL, Kassell NF, Schultz JR, Truskowski LL, Sigrest A. Cigarette smoking as a cause of aneurysmal subarachnoid hemorrhage and risk for vasospasm: A report of the cooperative aneurysm study. *Journal of neurosurgery*. 1998;89:405-411

97. Dupont SA, Wijdicks EF, Manno EM, Lanzino G, Rabinstein AA. Prediction of angiographic vasospasm after aneurysmal subarachnoid hemorrhage: Value of the hijdra sum scoring system. *Neurocritical care*. 2009;11:172-176

98. de Rooij NK, Rinkel GJ, Dankbaar JW, Frijns CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: A systematic review of clinical, laboratory, and radiological predictors. *Stroke*. 2013;44:43-54

99. Dasenbrock HH, Rudy RF, Lai PMR, Smith TR, Frerichs KU, Gormley WB, et al. Cigarette smoking and outcomes after aneurysmal subarachnoid hemorrhage: A nationwide analysis. *Journal of neurosurgery*. 2018;129:446-457

100. Lindbohm JV, Kaprio J, Korja M. Survival bias explains improved survival in smokers and hypertensive individuals after asah. *Neurology*. 2019;93:e2105-e2109

101. Juvela S. Alcohol consumption as a risk factor for poor outcome after aneurysmal subarachnoid haemorrhage. *British Medical Journal*. 1992;304:1663-1667

102. Morgan M, Halcrow S, Sorby W, Grinnell V. Outcome of aneurysmal subarachnoid haemorrhage following the introduction of papaverine angioplasty. *Journal of Clinical Neuroscience*. 1996;3:139-142

103. Group P. Determinants of poor outcome after aneurysmal subarachnoid hemorrhage when both clipping and coiling are available: Prospective registry of subarachnoid aneurysms treatment (presat) in japan. *World neurosurgery*. 2011;76:437-445

104. Schuss P, Hadjiathanasiou A, Borger V, Wispel C, Vatter H, Güresir E. Poor-grade aneurysmal subarachnoid hemorrhage: Factors influencing functional outcome—a single-center series. *World neurosurgery*. 2016;85:125-129

105. Takemoto Y, Hasegawa Y, Hashiguchi A, Moroki K, Tokuda H, Mukasa A. Predictors for functional outcome in patients with aneurysmal subarachnoid

hemorrhage who completed in-hospital rehabilitation in a single institution. *Journal of Stroke and Cerebrovascular Diseases*. 2019;28:1943-1950

106.   Øie LR, Solheim O, Majewska P, Nordseth T, Müller TB, Carlsen SM, et al. Incidence and case fatality of aneurysmal subarachnoid hemorrhage admitted to hospital between 2008 and 2014 in norway. *Acta Neurochirurgica*. 2020;162:2251-2259

107.   Lai PMR, Gormley WB, Patel N, Frerichs KU, Aziz-Sultan MA, Du R. Age-dependent radiographic vasospasm and delayed cerebral ischemia in women after aneurysmal subarachnoid hemorrhage. *World neurosurgery*. 2019;130:e230-e235

108.   Suarez JI, Sheikh MK, Macdonald RL, Amin-Hanjani S, Brown RD, de Oliveira Manoel AL, et al. Common data elements for unruptured intracranial aneurysms and subarachnoid hemorrhage clinical research: A national institute for neurological disorders and stroke and national library of medicine project. *Neurocritical care*. 2019;30:4-19

109.   Sheehan JP, Polin RS, Sheehan JM, Baskaya MK, Kassell NF. Factors associated with hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1999;45:1120-1128

110.   Dorai Z, Hynan LS, Kopitnik TA, Samson D. Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2003;52:763-771

111.   Alfotih GTA, Li F, Xu X, Zhang S. Risk factors for re-bleeding of aneurysmal subarachnoid hemorrhage: Meta-analysis of observational studies. *Neurologia i neurochirurgia polska*. 2014;48:346-355

112.   Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales. *Neurocritical care*. 2005;2:110-118

113.   van der Steen WE, Leemans EL, van den Berg R, Roos YB, Marquering HA, Verbaan D, et al. Radiological scales predicting delayed cerebral ischemia in subarachnoid hemorrhage: Systematic review and meta-analysis. *Neuroradiology*. 2019;61:247-256

114.   Drake C. Report of world federation of neurological surgeons committee on a universal subarachnoid hemorrhage grading scale. *J neurosurg*. 1988;68:985-986

115.   Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, Jr., et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified fisher scale. *Neurosurgery*. 2006;59:21-27; discussion 21-27

116.   de Oliveira Manoel AL, Goffi A, Marotta TR, Schweizer TA, Abrahamson S, Macdonald RL. The critical care management of poor-grade subarachnoid haemorrhage. *Critical care*. 2016;20:21

117.   Yoneda H, Nakamura T, Shirao S, Tanaka N, Ishihara H, Suehiro E, et al. Multicenter prospective cohort study on volume management after subarachnoid hemorrhage: Hemodynamic changes according to severity of subarachnoid hemorrhage and cerebral vasospasm. *Stroke*. 2013;44:2155-2161

118.   Zhang Q, Ma L, Liu Y, He M, Sun H, Wang X, et al. Timing of operation for poor-grade aneurysmal subarachnoid hemorrhage: Study protocol for a randomized controlled trial. *BMC neurology*. 2013;13:108

119.   Connolly Jr ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2012;43:1711-1737

120.   Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovascular diseases*. 2013;35:93-112

121.   Cortnum S, Sørensen P, Jørgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. *Neurosurgery*. 2010;66:900-903

122.   Pickard J, Murray G, Illingworth R, Shaw M, Teasdale G, Foy P, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *Bmj*. 1989;298:636-642

123.   Öhman J, Servo A, Heiskanen O. Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery. *Journal of neurosurgery*. 1991;74:8-13

124.   Natarajan S, Sekhar LN, Ghodke B, Britz GW, Bhagawati D, Temkin N. Outcomes of ruptured intracranial aneurysms treated by microsurgical clipping and endovascular coiling in a high-volume center. *American Journal of Neuroradiology*. 2008;29:753-759

125.   Phan HT, Gall SL, Blizzard CL, Lannin NA, Thrift AG, Anderson CS, et al. Sex differences in care and long-term mortality after stroke: Australian stroke clinical registry. *Journal of Women's Health*. 2019;28:712-720

126.   Gall S, Donnan G, Dewey H, Macdonell R, Sturm J, Gilligan A, et al. Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology*. 2010;74:975-981

127.   Madsen TE, Seigel TA, Mackenzie RS, Marcolini EG, Wira CR, Healy ME, et al. Gender differences in neurologic emergencies part i: A consensus summary and research agenda on cerebrovascular disease. *Academic Emergency Medicine*. 2014;21:1403-1413

128.   National institute of neurological disorders and stroke. Https://www.Ninds.Nih.Gov/disorders/patient-caregiver-education/fact-sheets/cerebral-aneurysms-fact-sheet#6. Accessed on nov 2, 2020.

129.   Alotaibi NM, Wang JZ, Pasarikovski CR, Guha D, Al-Mufti F, Mamdani M, et al. Management of raised intracranial pressure in aneurysmal subarachnoid hemorrhage: Time for a consensus? *Neurosurgical focus*. 2017;43:E13

130. Roquer J, Cuadrado-Godia E, Guimaraens L, Conesa G, Rodríguez-Campello A, Capellades J, et al. Short-and long-term outcome of patients with aneurysmal subarachnoid hemorrhage. *Neurology*. 2020;95:e1819-e1829

131. Anderson C, Ni Mhurchu C, Scott D, Bennett D, Jamrozik K, Hankey G. Triggers of subarachnoid hemorrhage: Role of physical exertion, smoking, and alcohol in the australasian cooperative research on subarachnoid hemorrhage study (across). *Stroke*. 2003;34:1771-1776

132. Karamanakos PN, Koivisto T, Vanninen R, Khallaf M, Ronkainen A, Parviainen I, et al. The impact of endovascular management on the outcome of aneurysmal subarachnoid hemorrhage in the elderly in eastern finland. *Acta neurochirurgica*. 2010;152:1493-1502

133. Ikawa F, Abiko M, Ishii D, Ohshita J, Matsushige T, Okazaki T, et al. Analysis of outcome at discharge after aneurysmal subarachnoid hemorrhage in japan according to the japanese stroke databank. *Neurosurgical review*. 2018;41:567-574

134. Fang Y, Lu J, Zheng J, Wu H, Araujo C, Reis C, et al. Comparison of aneurysmal subarachnoid hemorrhage grading scores in patients with aneurysm clipping and coiling. *Scientific Reports*. 2020;10:1-9

135. Rahmanian A, Jamali M, Bagheri Lankarani K, Ghahramani S. Aneurysmal subarachnoid haemorrhage (asah): Five consecutive years' experience of fars province, iran. *PloS one*. 2017;12:e0189005

136. Lee VH, Ouyang B, John S, Conners JJ, Garg R, Bleck TP, et al. Risk stratification for the in-hospital mortality in subarachnoid hemorrhage: The hair score. *Neurocritical care*. 2014;21:14-19

137. Lindekleiv H, Njølstad I, Ingebrigtsen T, Mathiesen E. Incidence of aneurysmal subarachnoid hemorrhage in norway, 1999–2007. *Acta neurologica Scandinavica*. 2011;123:34-40

138. van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. *The Lancet*. 2007;369:306-318

139. Wells GA SB, O'Connell D et al. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. Http://www.Ohri.Ca/programs/clinical_epidemiology/oxford.Asp. Accessed on sept 25, 2018.

140. White IR. Multivariate random-effects meta-analysis. *Stata Journal*. 2009;9:40-56

141. Adamski MG, Borratynska A, Krupa M, Wloch-Kopec D, Turaj W, Wolkow P, et al. A1/a2 polymorphism of gpiiia gene and a risk of aneurysmal subarachnoid haemorrhage. *Biochemical and biophysical research communications*. 2009;383:228-230

142. Anderson CS, Feigin V, Bennett D, Lin RB, Hankey G, Jamrozik K. Active and passive smoking and the risk of subarachnoid hemorrhage: An international population-based case-control study. *Stroke*. 2004;35:633-637

143.   Bell BA, Symon L. Smoking and subarachnoid haemorrhage. *British Medical Journal*. 1979;1:577-578

144.   Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, Dligach D, et al. Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. *Neurology*. 2017;89:1408-1415

145.   Canhao P, Pinto AN, Ferro H, Ferro JM. Smoking and aneurysmal subarachnoid haemorrhage: A case-control study. *Journal of cardiovascular risk*. 1994;1:155-158

146.   de Wilde AG, P.; Rinkel, G. J. E.; Algra, A. Stress and aneurysmal subarachnoid haemorrhage: Case control study. *Cerebrovascular Diseases* 2013;35:55

147.   Gaist D, Pedersen L, Cnattingius S, Sorensen HT. Parity and risk of subarachnoid hemorrhage in women: A nested case-control study based on national swedish registries. *Stroke*. 2004;35:28-32

148.   Hanson E, Olsson S, Bayazit B, Csajbok LZ, Nylen K, Nellgard B, et al. Association between variation in adamts13 and aneurysmal subarachnoid hemorrhage. *Thrombosis research*. 2013;131:99-101

149.   Inagawa T. Risk factors for aneurysmal subarachnoid hemorrhage in patients in izumo city, japan. *Journal of neurosurgery*. 2005;102:60-67

150.   Inagawa T. Risk factors for the formation and rupture of intracranial saccular aneurysms in shimane, japan. *World neurosurgery*. 2010;73:155-164; discussion e123

151.   Jimenez-Yepes CM, Londono-Fernandez JL. Risk of aneurysmal subarachnoid hemorrhage: The role of confirmed hypertension. *Stroke*. 2008;39:1344-1346

152.   Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. *Stroke*. 1993;24:639-646

153.   Kowalski R, Nyquist P. 472: Role of temperature and humidity in aneurysmal subarachnoid hemorrhage onset a comparative analysis. *Critical Care Medicine*. 2015;43:119-120

154.   Kubota M, Yamaura A, Ono J. Prevalence of risk factors for aneurysmal subarachnoid haemorrhage: Results of a japanese multicentre case control study for stroke. *British journal of neurosurgery*. 2001;15:474-478

155.   Ladenvall C, Csajbok L, Nylen K, Jood K, Nellgard B, Jern C. Association between factor xiii single nucleotide polymorphisms and aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2009;110:475-481

156.   Morris KM, Shaw MD, Foy PM. Smoking and subarachnoid haemorrhage: A case control study. *British journal of neurosurgery*. 1992;6:429-432

157.   Okamoto K, Horisawa R, Kawamura T, Asai A, Ogino M, Takagi T, et al. Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: A case-control study in nagoya, japan. *Stroke*. 2001;32:2841-2844

158. Okamoto K, Horisawa R, Kawamura T, Asai A, Ogino M, Takagi T, et al. Family history and risk of subarachnoid hemorrhage: A case-control study in nagoya, japan. *Stroke*. 2003;34:422-426

159. Okamoto K, Horisawa R, Ohno Y. The relationships of gender, cigarette smoking, and hypertension with the risk of aneurysmal subarachnoid hemorrhage: A case-control study in nagoya, japan. *Annals of epidemiology*. 2005;15:744-748

160. Olsson S, Csajbok LZ, Jood K, Nylen K, Nellgard B, Jern C. Association between genetic variation on chromosome 9p21 and aneurysmal subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery & Psychiatry*. 2011;82:384-388

161. Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. *Lancet (London, England)*. 1978;2:234-235

162. Ruiz-Sandoval JL, Cantu C, Chiquete E, Leon-Jimenez C, Arauz A, Murillo-Bonilla LM, et al. Aneurysmal subarachnoid hemorrhage in a mexican multicenter registry of cerebrovascular disease: The renamevasc study. *Journal of Stroke and Cerebrovascular Diseases*. 2009;18:48-55

163. Slowik A, Borratynska A, Pera J, Betlej M, Dziedzic T, Krzyszkowski T, et al. Ii genotype of the angiotensin-converting enzyme gene increases the risk for subarachnoid hemorrhage from ruptured aneurysm. *Stroke*. 2004;35:1594-1597

164. Staalso JM, Edsen T, Kotinis A, Romner B, Springborg JB, Olsen NV. Association of the nos3 intron-4 vntr polymorphism with aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2014;121:587-592

165. Vlak MH, Rinkel GJ, Greebe P, Greving JP, Algra A. Lifetime risks for aneurysmal subarachnoid haemorrhage: Multivariable risk stratification. *Journal of Neurology, Neurosurgery & Psychiatry*. 2013;84:619-623

166. You S-H, Kong D-S, Kim J-S, Jeon P, Kim KH, Roh HK, et al. Characteristic features of unruptured intracranial aneurysms: Predictive risk factors for aneurysm rupture. *Journal of Neurology, Neurosurgery & Psychiatry*. 2010;81:479-484

167. Lindegård B, Hillbom M, Brody S. High-dose estrogen-progestagen oral contraceptives: A risk factor for aneurysmal subarachnoid hemorrhage? *Acta neurologica Scandinavica*. 1987;76:37-45

168. Sandvei MS, Romundstad PR, Müller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: The hunt study in norway. *Stroke*. 2009;40:1958-1962

169. Sandvei MS, Lindekleiv H, Romundstad PR, Muller TB, Vatten LJ, Ingebrigtsen T, et al. Risk factors for aneurysmal subarachnoid hemorrhage - bmi and serum lipids: 11-year follow-up of the hunt and the tromso study in norway. *Acta neurologica Scandinavica*. 2012;125:382-388

170. Tabuchi S. Relationship between postmenopausal estrogen deficiency and aneurysmal subarachnoid hemorrhage. *Behavioural neurology*. 2015;2015

171. Wang YX, He J, Zhang L, Li Y, Zhao L, Liu H, et al. A higher aneurysmal subarachnoid hemorrhage incidence in women prior to menopause: A retrospective analysis of 4,895 cases from eight hospitals in china. *Quantitative imaging in medicine and surgery*. 2016;6:151-156

172. Andreasen TH, Bartek J, Andresen M, Springborg JB, Romner B. Modifiable risk factors for aneurysmal subarachnoid hemorrhage. *Stroke*. 2013;44:3607-3612

173. Handa H, Hashimoto N, Nagata I, Hazama F. Saccular cerebral aneurysms in rats: A newly developed animal model of the disease. *Stroke*. 1983;14:857-866

174. Tada Y, Makino H, Furukawa H, Shimada K, Wada K, Liang EI, et al. Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice. *Neurosurgery*. 2014;75:690-695

175. Johnston SC, Colford JM, Jr., Gress DR. Oral contraceptives and the risk of subarachnoid hemorrhage: A meta-analysis. *Neurology*. 1998;51:411-418

176. Mhurchu CN, Anderson C, Jamrozik K, Hankey G, Dunbabin D. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: An international population-based, case-control study. *Stroke*. 2001;32:606-612

177. Chalouhi N, Ali MS, Starke RM, Jabbour PM, Tjoumakaris SI, Gonzalez LF, et al. Cigarette smoke and inflammation: Role in cerebral aneurysm formation and rupture. *Mediators of inflammation*. 2012;2012

178. Leeman MF, Curran S, Murray GI. The structure, regulation, and function of human matrix metalloproteinase-13. *Critical reviews in biochemistry and molecular biology*. 2002;37:149-166

179. Starke RM, Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, et al. The role of oxidative stress in cerebral aneurysm formation and rupture. *Current neurovascular research*. 2013;10:247-255

180. Zheng XL. Adamts13 and von willebrand factor in thrombotic thrombocytopenic purpura. *Annual review of medicine*. 2015;66:211-225

181. Krishnan R, Sekar D, Subramanium S. Association of angiotensin converting enzyme gene insertion/deletion polymorphism with essential hypertension in south indian population. *Genes & Diseases*. 2016;3:159-163

182. Dhar S, Ray S, Dutta A, Sengupta B, Chakrabarti S. Polymorphism of ace gene as the genetic predisposition of coronary artery disease in eastern india. *Indian heart journal*. 2012;64:576-581

183. Zhang Z, Xu G, Liu D, Fan X, Zhu W, Liu X. Angiotensin-converting enzyme insertion/deletion polymorphism contributes to ischemic stroke risk: A meta-analysis of 50 case-control studies. *PLoS one*. 2012;7:e46495

184. Santana NMT, Mill JG, Velasquez-Melendez G, Moreira AD, Barreto SM, Viana MC, et al. Consumption of alcohol and blood pressure: Results of the elsa-brasil study. *PLoS One*. 2018;13:e0190239

185. Ohkuma H, Tabata H, Suzuki S, Islam MS. Risk factors for aneurysmal subarachnoid hemorrhage in aomori, japan. *Stroke*. 2003;34:96-100

186. Parikh NS, Merkler AE, Jesudian A, Kamel H. Association between cirrhosis and aneurysmal subarachnoid hemorrhage. *Annals of Clinical and Translational Neurology*. 2019;6:27-32

187. Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. *Current vascular pharmacology*. 2012;10:4-18

188. Ariëns RA, Lai T-S, Weisel JW, Greenberg CS, Grant PJ. Role of factor xiii in fibrin clot formation and effects of genetic polymorphisms. *Blood*. 2002;100:743-754

189. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, Manolescu A, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nature genetics*. 2008;40:217

190. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al. Genomewide association analysis of coronary artery disease. *New England Journal of Medicine*. 2007;357:443-453

191. Matarin M, Brown WM, Singleton A, Hardy JA, Meschia JF. Whole genome analyses suggest ischemic stroke and heart disease share an association with polymorphisms on chromosome 9p21. *Stroke*. 2008;39:1586-1589

192. Yao X-Y, Jiang C-Q, Jia G-L, Chen G. Diabetes mellitus and the risk of aneurysmal subarachnoid haemorrhage: A systematic review and meta-analysis of current evidence. *Journal of International Medical Research*. 2016;44:1141-1155

193. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: A systematic review and meta-analysis. *The Lancet Neurology*. 2011;10:626-636

194. Rosenørn J, Eskesen V, Schmidt K. Clinical features and outcome in females and males with ruptured intracranial saccular aneurysms. *British journal of neurosurgery*. 1993;7:287-290

195. Vergouwen MD, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and-independent effects. *Stroke*. 2011;42:924-929

196. Chotai S, Ahn SY, Moon HJ, Kim JH, Chung HS, Chung YG, et al. Prediction of outcomes in young adults with aneurysmal subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)*. 2013;53:157-162

197. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex differences in long-term mortality after stroke in the instruct (international stroke outcomes study) a meta-analysis of individual participant data. *Circulation: Cardiovascular Quality and Outcomes*. 2017;10:e003436

198. Rowland M, Hadjipavlou G, Kelly M, Westbrook J, Pattinson K. Delayed cerebral ischaemia after subarachnoid haemorrhage: Looking beyond vasospasm. *British journal of anaesthesia*. 2012;109:315-329

199. Germans MR, Jaja BN, de Oliviera Manoel AL, Cohen AH, Macdonald RL. Sex differences in delayed cerebral ischemia after subarachnoid hemorrhage. *Journal of neurosurgery*. 2018;129:458-464

200. Duan W, Pan Y, Wang C, Wang Y, Zhao X, Wang Y, et al. Risk factors and clinical impact of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Analysis from the china national stroke registry. *Neuroepidemiology*. 2018;50:128-136

201. Rooij NKd, Rinkel GJE, Dankbaar JW, Frijns CJM. Delayed cerebral ischemia after subarachnoid hemorrhage. *Stroke*. 2013;44:43-54

202. Cha KC, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS. Aneurysmal rebleeding: Factors associated with clinical outcome in the rebleeding patients. *Journal of Korean Neurosurgical Society*. 2010;47:119

203. Buczacki S, Kirkpatrick P, Seeley H, Hutchinson P. Late epilepsy following open surgery for aneurysmal subarachnoid haemorrhage. *Journal of Neurology, Neurosurgery & Psychiatry*. 2004;75:1620-1622

204. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (redcap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42:377-381

205. Bijlenga P, Gondar R, Schilling S, Morel S, Hirsch S, Cuony J, et al. Phases score for the management of intracranial aneurysm: A cross-sectional population-based retrospective study. *Stroke*. 2017;48:2105-2112

206. Greenland S. Modeling and variable selection in epidemiologic analysis. *American journal of public health*. 1989;79:340-349

207. Zheng K, Zhong M, Zhao B, Chen S-Y, Tan X-X, Li Z-Q, et al. Poor-grade aneurysmal subarachnoid hemorrhage: Risk factors affecting clinical outcomes in intracranial aneurysm patients in a multi-center study. *Frontiers in Neurology*. 2019;10:123

208. Vale FL, Bradley EL, Fisher WS, 3rd. The relationship of subarachnoid hemorrhage and the need for postoperative shunting. *J Neurosurg*. 1997;86:462-466

209. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Critical Care*. 2016;20:277

210. Shishido H, Zhang H, Okubo S, Hua Y, Keep RF, Xi G. The effect of gender on acute hydrocephalus after experimental subarachnoid hemorrhage. *Brain edema xvi*. Springer; 2016:335-339.

211. Aarhus M, Helland CA, Wester K. Differences in anatomical distribution, gender, and sidedness between ruptured and unruptured intracranial aneurysms in a defined patient population. *Acta Neurochirurgica*. 2009;151:1569

212. Lin B, Chen W, Ruan L, Chen Y, Zhong M, Zhuge Q, et al. Sex differences in aneurysm morphologies and clinical outcomes in ruptured anterior communicating artery aneurysms: A retrospective study. *BMJ open*. 2016;6:e009920

213. He Z, Wan Y. Is fetal-type posterior cerebral artery a risk factor for intracranial aneurysm as analyzed by multislice ct angiography? *Experimental and therapeutic medicine*. 2018;15:838-846

214. Horikoshi T, Akiyama I, Yamagata Z, Sugita M, Nukui H. Magnetic resonance angiographic evidence of sex-linked variations in the circle of willis and the occurrence of cerebral aneurysms. 2002;96:697

215. Zhao X, Zhao M, Amin-Hanjani S, Du X, Ruland S, Charbel FT. Wall shear stress in major cerebral arteries as a function of age and gender—a study of 301 healthy volunteers. *Journal of Neuroimaging*. 2015;25:403-407

216. Wouter IS, Eelco FMW, David GP, Chu-Pin C, O'Fallon WM, Jack PW. The poor prognosis of ruptured intracranial aneurysms of the posterior circulation. *Journal of Neurosurgery*. 1995;82:791-795

217. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Risk factors of sudden death from subarachnoid hemorrhage. *Stroke*. 2017;48:2399-2404

218. D'Souza S. Aneurysmal subarachnoid hemorrhage. *Journal of neurosurgical anesthesiology*. 2015;27:222

219. Ferguson S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2007;60:658-667

220. Sanelli PC, Anumula N, Gold R, Elias E, Johnson C, Comunale J, et al. Outcomes-based assessment of a new reference standard for delayed cerebral ischemia related to vasospasm in aneurysmal subarachnoid hemorrhage. *Academic radiology*. 2012;19:1066-1074

221. Adams H, Ban VS, Leinonen V, Aoun SG, Huttunen J, Saavalainen T, et al. Risk of shunting after aneurysmal subarachnoid hemorrhage. *Stroke*. 2016;47:2488-2496

222. Awe OO, Gonzalez LF, Hasan D, Maltenfort M, Rossenwasser R, Jabbour P. Treatment outcome of aneurysmal subarachnoid hemorrhage in patients aged 70 years and older. *Neurosurgery*. 2011;68:753-758

223. Budohoski KP, Guilfoyle M, Helmy A, Huuskonen T, Czosnyka M, Kirollos R, et al. The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 2014;85:1343-1353

224. Lantigua H, Ortega-Gutierrez S, Schmidt JM, Lee K, Badjatia N, Agarwal S, et al. Subarachnoid hemorrhage: Who dies, and why? *Critical Care*. 2015;19:309

225.   Hubbard IJ, Harris D, Kilkenny MF, Faux SG, Pollack MR, Cadilhac DA. Adherence to clinical guidelines improves patient outcomes in australian audit of stroke rehabilitation practice. *Archives of physical medicine and rehabilitation*. 2012;93:965-971

226.   Tang C, Zhang T-S, Zhou L-F. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: A meta-analysis. *PLoS One*. 2014;9:e99536

227.   Ido MS, Frankel MR, Okosun IS, Rothenberg RB. Quality of care and its impact on one-year mortality: The georgia coverdell acute stroke registry. *American journal of medical quality : the official journal of the American College of Medical Quality*. 2018;33:86-92

228.   van Heuven AW, Dorhout Mees SM, Algra A, Rinkel GJ. Validation of a prognostic subarachnoid hemorrhage grading scale derived directly from the glasgow coma scale. *Stroke*. 2008;39:1347-1348

229.   Fisher C, Kistler J, Davis J. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery*. 1980;6:1-9

230.   Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified fisher scale. *Neurosurgery*. 2006;59:21-27

231.   Bar B, Hemphill III JC. Charlson comorbidity index adjustment in intracerebral hemorrhage. *Stroke*. 2011;42:2944-2946

232.   Rehman S, Chandra RV, Zhou K, Tan D, Lai L, Asadi H, et al. Sex differences in aneurysmal subarachnoid haemorrhage (asah): Aneurysm characteristics, neurological complications, and outcome. *Acta Neurochirurgica*. 2020;162:2271-2282

233.   Mogensen UB, Olsen TS, Andersen KK, Gerds TA. Cause-specific mortality after stroke: Relation to age, sex, stroke severity, and risk factors in a 10-year follow-up study. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2013;22:e59-65

234.   Goldberg J, Schoeni D, Mordasini P, Z'graggen W, Gralla J, Raabe A, et al. Survival and outcome after poor-grade aneurysmal subarachnoid hemorrhage in elderly patients. *Stroke*. 2018;49:2883-2889

235.   Cavanagh SJ, Gordon VL. Grading scales used in the management of aneurysmal subarachnoid hemorrhage: A critical review. *Journal of Neuroscience Nursing*. 2002;34:288-296

236.   Kowalski RG, Chang TR, Carhuapoma JR, Tamargo RJ, Naval NS. Withdrawal of technological life support following subarachnoid hemorrhage. *Neurocritical care*. 2013;19:269-275

237.   Degen LA, Dorhout Mees SM, Algra A, Rinkel GJ. Interobserver variability of grading scales for aneurysmal subarachnoid hemorrhage. *Stroke*. 2011;42:1546-1549

238. Wostrack M, Sandow N, Vajkoczy P, Schatlo B, Bijlenga P, Schaller K, et al. Subarachnoid haemorrhage wfns grade v: Is maximal treatment worthwhile? *Acta neurochirurgica*. 2013;155:579-586

239. Das JM, Zito PM. Nimodipine. *Statpearls [internet]*. StatPearls Publishing; 2018.

240. Korja M, Kivisaari R, Rezai Jahromi B, Lehto H. Natural history of ruptured but untreated intracranial aneurysms. *Stroke*. 2017;48:1081-1084

241. Muñoz Venturelli P, Li X, Middleton S, Watkins C, Lavados PM, Olavarría VV, et al. Impact of evidence-based stroke care on patient outcomes: A multilevel analysis of an international study. *Journal of the American Heart Association*. 2019;8:e012640

242. Harris D, Cadilhac DA, Hankey GJ, Hillier S, Kilkenny M, Lalor E. National stroke audit: The australian experience. *Clinical Audit*. 2010;2:25

243. Zheng K, Zhao B, Tan X-X, Li Z-Q, Xiong Y, Zhong M, et al. Comparison of aggressive surgical treatment and palliative treatment in elderly patients with poor-grade intracranial aneurysmal subarachnoid hemorrhage. *BioMed research international*. 2018;2018

244. Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: Functional outcomes, handicap, and quality of life. *Stroke*. 2012;43:1982-1987

245. Fukuda M, Kanda T, Kamide N, Akutsu T, Sakai F. Gender differences in long-term functional outcome after first-ever ischemic stroke. *Internal Medicine*. 2009;48:967-973

246. Dabilgou AA, Drave A, Kyelem JMA, Naon L, Napon C, Kabore J. Spontaneous subarachnoid haemorrhage in neurological setting in burkina faso: Clinical profile, causes, and mortality risk factors. *Neurology research international*. 2019;2019

247. Sudlow C, Warlow C. Comparing stroke incidence worldwide: What makes studies comparable? *Stroke*. 1996;27:550-558

248. Malmgren R, Bamford J, Warlow C, Sandercock P. Geographical and secular trends in stroke incidence. *The Lancet*. 1987;330:1196-1200

249. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, et al. Factors contributing to sex differences in functional outcomes and participation after stroke. *Neurology*. 2018;90:e1945-e1953

250. Moro CH, Gonçalves AR, Longo AL, Fonseca PG, Harger R, Gomes DB, et al. Trends of the incidence of ischemic stroke thrombolysis over seven years and one-year outcome: A population-based study in joinville, brazil. *Cerebrovascular diseases extra*. 2013;3:156-166

251. Vemmos KN, Bots M, Tsibouris P, Zis V, Takis C, Grobbee D, et al. Prognosis of stroke in the south of greece: 1 year mortality, functional outcome and its

determinants: The arcadia stroke registry. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;69:595-600

252. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the perth community stroke study. *Stroke*. 2000;31:2080-2086

253. Appelros P, Nydevik I, Seiger Å, Terént A. High incidence rates of stroke in örebro, sweden: Further support for regional incidence differences within scandinavia. *Cerebrovascular Diseases*. 2002;14:161-168

254. Correia M, Magalhães R, Silva MR, Matos I, Silva MC. Stroke types in rural and urban northern portugal: Incidence and 7-year survival in a community-based study. *Cerebrovascular diseases extra*. 2013;3:137-149

255. Carolei A, Marini C, Di Napoli M, Di Gianfilippo G, Santalucia P, Baldassarre M, et al. High stroke incidence in the prospective community-based l'aquila registry (1994–1998) first year's results. *Stroke*. 1997;28:2500-2506

256. Minelli C, Fu Fen L, Camara Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in matao, brazil: A population-based prospective study. *Stroke*. 2007;38:2906-2911

257. Vibo R, Korv J, Roose M. One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from tartu, estonia. *European journal of neurology*. 2007;14:435-439

258. Chausson N, Olindo Sp, Cabre P, Saint-Vil M, Smadja D. Five-year outcome of a stroke cohort in martinique, french west indies: Etude realisee en martinique et centree sur l'incidence des accidents vasculaires cerebraux, part 2. *Stroke*. 2010;41:594-599

259. Rothwell P, Coull A, Giles M, Howard S, Silver L, Bull L, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in oxfordshire, uk from 1981 to 2004 (oxford vascular study). *The Lancet*. 2004;363:1925-1933

260. Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in dijon, france, from 1989 to 2006: A population-based study. *Stroke*. 2008;39:1945-1951

261. Feigin V, Barker-Collo S, Parag V, Senior H, Lawes C, Ratnasabapathy Y, et al. Auckland stroke outcomes study: Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. *Neurology*. 2010;75:1597-1607

262. Bahit MC, Coppola ML, Riccio PM, Cipriano LE, Roth GA, Lopes RD, et al. First-ever stroke and transient ischemic attack incidence and 30-day case-fatality rates in a population-based study in argentina. *Stroke*. 2016;47:1640-1642

263. Pandian JD, Singh G, Kaur P, Bansal R, Paul BS, Singla M, et al. Incidence, short-term outcome, and spatial distribution of stroke patients in ludhiana, india. *Neurology*. 2016;86:425-433

264.   Farzadfard MT, Thrift AG, Amiri A, Kapral MK, Hashemi P, Sposato LA, et al. Five-year case fatality following first-ever stroke in the mashhad stroke incidence study: A population-based study of stroke in the middle east. *Journal of Stroke and Cerebrovascular Diseases*. 2018;27:1085-1089

265.   Sweeney K, Silver N, Javadpour M. Subarachnoid haemorrhage (spontaneous aneurysmal). *BMJ Clin Evid*. 2016;2016:1213

266.   Quinn T, Dawson J, Walters M, Lees K. Functional outcome measures in contemporary stroke trials. *International Journal of Stroke*. 2009;4:200-205

267.   Uyttenboogaart M, Luijckx GJ, Vroomen PC, Stewart RE, De Keyser J. Measuring disability in stroke: Relationship between the modified rankin scale and the barthel index. *Journal of neurology*. 2007;254:1113-1117

268.   Farzadfard MT, Sheikh Andalibi MS, Thrift AG, Morovatdar N, Stranges S, Amiri A, et al. Long-term disability after stroke in iran: Evidence from the mashhad stroke incidence study. *International journal of stroke : official journal of the International Stroke Society*. 2019;14:44-47

269.   Phan HT, Reeves MJ, Blizzard CL, Thrift AG, Cadilhac DA, Sturm J, et al. Sex differences in severity of stroke in the instruct study: A meta-analysis of individual participant data. *J Am Heart Assoc*. 2019;8:e010235-e010235

270.   Tsao JW, Hemphill JC, Johnston SC, Smith WS, Bonovich DC. Initial glasgow coma scale score predicts outcome following thrombolysis for posterior circulation stroke. *Archives of neurology*. 2005;62:1126-1129

271.   Wu S, Yuan R, Xiong Y, Zhang S, Wu B, Liu M. Clinical features, management and outcomes of severe ischaemic stroke in tertiary hospitals in china: Protocol for a prospective multicentre registry-based observational study. *BMJ open*. 2018;8:e024900

272.   Molyneux AJ, Kerr RS, Yu L-M, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (isat) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *The Lancet*. 2005;366:809-817

273.   Rackauskaite D, Svanborg E, Andersson E, Löwhagen K, Csajbok L, Nellgård B. Prospective study: Long-term outcome at 12-15 years after aneurysmal subarachnoid hemorrhage. *Acta Neurologica Scandinavica*. 2018;138:400-407

274.   Waweru P, Gatimu SM. Mortality and functional outcomes after a spontaneous subarachnoid haemorrhage: A retrospective multicentre cross-sectional study in kenya. *PloS one*. 2019;14:e0217832

275.   Rahmanian A, Derakhshan N, Sisakht AM, Ziarati NK, Shahraki HR, Motamed S. Risk factors for unfavorable outcome in aneurysmal subarachnoid hemorrhage revisited; odds and ends. *Bulletin of Emergency & Trauma*. 2018;6:133

276. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Kaprio J. Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage. *Neurology*. 2013;80:481-486

277. McIntyre MK, Gandhi C, Long A, Van Hoof A, Li B, Patel V, et al. Age predicts outcomes better than frailty following aneurysmal subarachnoid hemorrhage: A retrospective cohort analysis. *Clinical neurology and neurosurgery*. 2019;187:105558

278. Sodhi HBS, Savardekar AR, Mohindra S, Chhabra R, Gupta V, Gupta SK. The clinical profile, management, and overall outcome of aneurysmal subarachnoid hemorrhage at the neurosurgical unit of a tertiary care center in india. *Journal of neurosciences in rural practice*. 2014;5:118-126

279. Hanel RA, Xavier AR, Mohammad Y, Kirmani JF, Yahia AM, Qureshi AI. Outcome following intracerebral hemorrhage and subarachnoid hemorrhage. *Neurological research*. 2002;24:58-62

280. Helbok R, Kurtz P, Vibbert M, Schmidt MJ, Fernandez L, Lantigua H, et al. Early neurological deterioration after subarachnoid haemorrhage: Risk factors and impact on outcome. *J Neurol Neurosurg Psychiatry*. 2013;84:266-270

281. Park J, Woo H, Kang D-H, Kim Y. Critical age affecting 1-year functional outcome in elderly patients aged ≥ 70 years with aneurysmal subarachnoid hemorrhage. *Acta neurochirurgica*. 2014;156:1655-1661

282. Degos V, Gourraud P-A, Tursis VT, Whelan R, Colonne C, Korinek AM, et al. Elderly age as a prognostic marker of 1-year poor outcome for subarachnoid hemorrhage patients through its interaction with admission hydrocephalus. *Survey of Anesthesiology*. 2013;57:180-181

283. Yue Q, Liu Y, Leng B, Xu B, Gu Y, Chen L, et al. A prognostic model for early post-treatment outcome of elderly patients with aneurysmal subarachnoid hemorrhage. *World neurosurgery*. 2016;95:253-261

284. Zheng J, Sun X, Zhang X. Influence of age-related complications on clinical outcome in patients with small ruptured cerebral aneurysms. *Frontiers in Neurology*. 2020;11

285. Tawk RG, Grewal SS, Heckman MG, Navarro R, Ferguson JL, Starke EL, et al. Influence of body mass index and age on functional outcomes in patients with subarachnoid hemorrhage. *Neurosurgery*. 2015;76:136-141

286. Sugawara T, Maehara T, Nariai T, Aoyagi M, Ohno K. Independent predictors of shunt-dependent normal pressure hydrocephalus after aneurysmal subarachnoid hemorrhage. *Journal of neurosurgical sciences*. 2016;60:154-158

287. Guo L-m, Zhou H-y, Xu J-w, Wang Y, Qiu Y-m, Jiang J-y. Risk factors related to aneurysmal rebleeding. *World neurosurgery*. 2011;76:292-298

288. Horie N, Sato S, Kaminogo M, Morofuji Y, Izumo T, Anda T, et al. Impact of perioperative aneurysm rebleeding after subarachnoid hemorrhage. *Journal of neurosurgery*. 2019;1:1-10

289. Ryttlefors M, Enblad P. Subarachnoid haemorrhage in the elderly. In: Berhouma M, Krolak-Salmon P, eds. *Brain and spine surgery in the elderly*. Cham: Springer International Publishing; 2017:375-410.

290. Gizewski E, Göricke S, Wolf A, Schoch B, Stolke D, Forsting M, et al. Endovascular treatment of intracranial aneurysms in patients 65 years or older: Clinical outcomes. *American journal of neuroradiology*. 2008;29:1575-1580

291. Luo C-B, Teng MM-H, Chang F-C, Chang C-Y. Endovascular embolization of ruptured cerebral aneurysms in patients older than 70 years. *Journal of clinical neuroscience*. 2007;14:127-132

292. Mocco J, Ransom ER, Komotar RJ, Schmidt JM, Sciacca RR, Mayer SA, et al. Preoperative prediction of long-term outcome in poor-grade aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2006;59:529-538

293. Risselada R, Lingsma H, Bauer-Mehren A, Friedrich C, Molyneux A, Kerr R, et al. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: Results from the international subarachnoid aneurysm trial (isat). *European journal of epidemiology*. 2010;25:261-266

294. Dhandapani S, Singh A, Singla N, Praneeth K, Aggarwal A, Sodhi HB, et al. Has outcome of subarachnoid hemorrhage changed with improvements in neurosurgical services? Study of 2000 patients over 2 decades from india. *Stroke*. 2018;49:2890-2895

295. Pegoli M, Mandrekar J, Rabinstein AA, Lanzino G. Predictors of excellent functional outcome in aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2015;122:414-418

296. Ezzati M, Lopez AD. Regional, disease specific patterns of smoking-attributable mortality in 2000. *Tobacco control*. 2004;13:388-395

297. Bøthun ML, Haaland ØA, Moen G, Logallo N, Svendsen F, Thomassen L, et al. Impaired cerebrovascular reactivity may predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Journal of the neurological sciences*. 2019;407:116539

298. Olsen MH, Orre M, Leisner ACW, Rasmussen R, Bache S, Welling KL, et al. Delayed cerebral ischaemia in patients with aneurysmal subarachnoid haemorrhage: Functional outcome and long‐term mortality. *Acta Anaesthesiologica Scandinavica*. 2019;63:1191-1199

299. Futchko J, Starr J, Lau D, Leach MR, Roark C, Pandey AS, et al. Influence of smoking on aneurysm recurrence after endovascular treatment of cerebrovascular aneurysms. *Journal of neurosurgery*. 2018;128:992-998

300. Lovelock C, Rinkel G, Rothwell P. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. *Neurology*. 2010;74:1494-1501

301.   Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology*. 1998;50:1413-1418

302.   Tang C, Zhang T-S, Zhou L-F. Risk factors for rebleeding of aneurysmal subarachnoid hemorrhage: A meta-analysis. *PLoS One*. 2014;9

303.   Juvela S, Siironen J, Kuhmonen J. Hyperglycemia, excess weight, and history of hypertension as risk factors for poor outcome and cerebral infarction after aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2005;102:998-1003

304.   Lasner TM, Weil RJ, Riina HA, King JT, Zager EL, Raps EC, et al. Cigarette smoking—induced increase in the risk of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 1997;87:381-384

305.   Chan M, Alaraj A, Calderon M, Herrera SR, Gao W, Ruland S, et al. Prediction of ventriculoperitoneal shunt dependency in patients with aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery*. 2009;110:44-49

306.   Aboul-Ela HM, El-Din AMS, Zaater AA, Shehab M, El Shahawy OA. Predictors of shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: A pilot study in a single egyptian institute. *The Egyptian journal of neurology, psychiatry and neurosurgery*. 2018;54:11

307.   Kwon J-H, Sung S-K, Song Y-J, Choi H-J, Huh J-T, Kim H-D. Predisposing factors related to shunt-dependent chronic hydrocephalus after aneurysmal subarachnoid hemorrhage. *Journal of Korean Neurosurgical Society*. 2008;43:177

308.   Paisan GM, Ding D, Starke RM, Crowley RW, Liu KC. Shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: Predictors and long-term functional outcomes. *Neurosurgery*. 2018;83:393-402

309.   Qureshi AI, Malik AA, Saeed O, Defillo A, Sherr GT, Suri MFK. Hormone replacement therapy and the risk of subarachnoid hemorrhage in postmenopausal women. *Journal of neurosurgery*. 2016;124:45-50

310.   Maekawa H, Tada Y, Yagi K, Miyamoto T, Kitazato KT, Korai M, et al. Bazedoxifene, a selective estrogen receptor modulator, reduces cerebral aneurysm rupture in ovariectomized rats. *Journal of Neuroinflammation*. 2017;14:197

311.   Australian stroke clinical registry. Https://auscr.Com.Au/health-professionals/variables-program-bundles. Accessed on nov 24, 2020.

312.   Lin C-L, Shih H-C, Dumont AS, Kassell NF, Lieu A-S, Su Y-F, et al. The effect of 17β-estradiol in attenuating experimental subarachnoid hemorrhage–induced cerebral vasospasm. *Journal of neurosurgery*. 2006;104:298-304

313.   Shih H-C, Lin C-L, Lee T-Y, Lee W-S, Hsu C. 17β-estradiol inhibits subarachnoid hemorrhage–induced inducible nitric oxide synthase gene expression by interfering with the nuclear factor κb transactivation. *Stroke*. 2006;37:3025-3031

314. Ding D, Starke RM, Dumont AS, Owens GK, Hasan DM, Chalouhi N, et al. Therapeutic implications of estrogen for cerebral vasospasm and delayed cerebral ischemia induced by aneurysmal subarachnoid hemorrhage. *BioMed research international*. 2014;2014

315. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: A prospective finnish cohort study. *Stroke*. 2014;45:1958-1963

316. Hackenberg KA, Hänggi D, Etminan N. Unruptured intracranial aneurysms: Contemporary data and management. *Stroke*. 2018;49:2268-2275

317. Darsaut TE, Findlay JM, Magro E, Kotowski M, Roy D, Weill A, et al. Surgical clipping or endovascular coiling for unruptured intracranial aneurysms: A pragmatic randomised trial. *Journal of Neurology, Neurosurgery & Psychiatry*. 2017;88:663-668

318. Weng J-C, Wang J, Li H, Jiao Y-M, Fu W-L, Huo R, et al. Aspirin and growth of small unruptured intracranial aneurysm. *Stroke*. 2020;51:3045-3054

319. Giordan E, Graffeo CS, Rabinstein AA, Brown RD, Rocca WA, Chamberlain AM, et al. Aneurysmal subarachnoid hemorrhage: Long-term trends in incidence and survival in olmsted county, minnesota. *Journal of neurosurgery*. 2020;1:1-6

320. Chan V, Lindsay P, McQuiggan J, Zagorski B, Hill MD, O'Kelly C. Declining admission and mortality rates for subarachnoid hemorrhage in canada between 2004 and 2015. *Stroke*. 2019;50:181-184

321. Nicholson P, O'Hare A, Power S, Looby S, Javadpour M, Thornton J, et al. Decreasing incidence of subarachnoid hemorrhage. *Journal of neurointerventional surgery*. 2019;11:320-322

322. Anetsberger A, Gempt J, Blobner M, Ringel F, Bogdanski R, Heim M, et al. Impact of goal-directed therapy on delayed ischemia after aneurysmal subarachnoid hemorrhage: Randomized controlled trial. *Stroke*. 2020;51:2287-2296

323. Gathier CS, van den Bergh WM, van der Jagt M, Verweij BH, Dankbaar JW, Müller MC, et al. Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: A randomized clinical trial. *Stroke*. 2018;49:76-83

324. Matsuda N, Naraoka M, Ohkuma H, Shimamura N, Ito K, Asano K, et al. Effect of cilostazol on cerebral vasospasm and outcome in patients with aneurysmal subarachnoid hemorrhage: A randomized, double-blind, placebo-controlled trial. *Cerebrovascular Diseases*. 2016;42:97-105

325. Luo M, Yang S, Ding G, Xiao Q. Endovascular coiling versus surgical clipping for aneurysmal subarachnoid hemorrhage: A meta-analysis of randomized controlled trials. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2019;24

326. Stroke foundation. Https://strokefoundation.Org.Au/what-we-do/treatment-programs/clinical-guidelines. Accessed on nov 23, 2020.

327. Smith E, Liang L, Hernandez A, Reeves M, Cannon C, Fonarow G, et al. Influence of stroke subtype on quality of care in the get with the guidelines–stroke program. *Neurology*. 2009;73:709-716

328. Get with the guidelines® - stroke patient management tool. Https://www.Heart.Org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-stroke/get-with-the-guidelines-stroke-patient-management-tool. Accessed on nov 24, 2020.

329. Wiborg A, Widder B. Teleneurology to improve stroke care in rural areas: The telemedicine in stroke in swabia (tess) project. *Stroke*. 2003;34:2951-2956

330. Hov MR, Ryen A, Finsnes K, Storflor J, Lindner T, Gleditsch J, et al. Pre-hospital ct diagnosis of subarachnoid hemorrhage. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2017;25:1-4

331. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, et al. Lifestyle interventions to reduce raised blood pressure: A systematic review of randomized controlled trials. *Journal of hypertension*. 2006;24:215-233

332. Eliasson B, Hjalmarson A, Kruse E, Landfeldt B, Westin Å. Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine & Tobacco Research*. 2001;3:249-255

333. Kalkonde YV, Alladi S, Kaul S, Hachinski V. Stroke prevention strategies in the developing world. *Stroke*. 2018;49:3092-3097

334. Abascal W, Esteves E, Goja B, Mora FG, Lorenzo A, Sica A, et al. Tobacco control campaign in uruguay: A population-based trend analysis. *The Lancet*. 2012;380:1575-1582

335. Stroke foundation. Https://strokefoundation.Org.Au/en/what-we-do/prevention-programs/national-stroke-week. Accessed on nov 24, 2020.

336. Stroke riskometer. Https://www.Strokeriskometer.Com. Accessed on nov 24, 2020.