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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 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.

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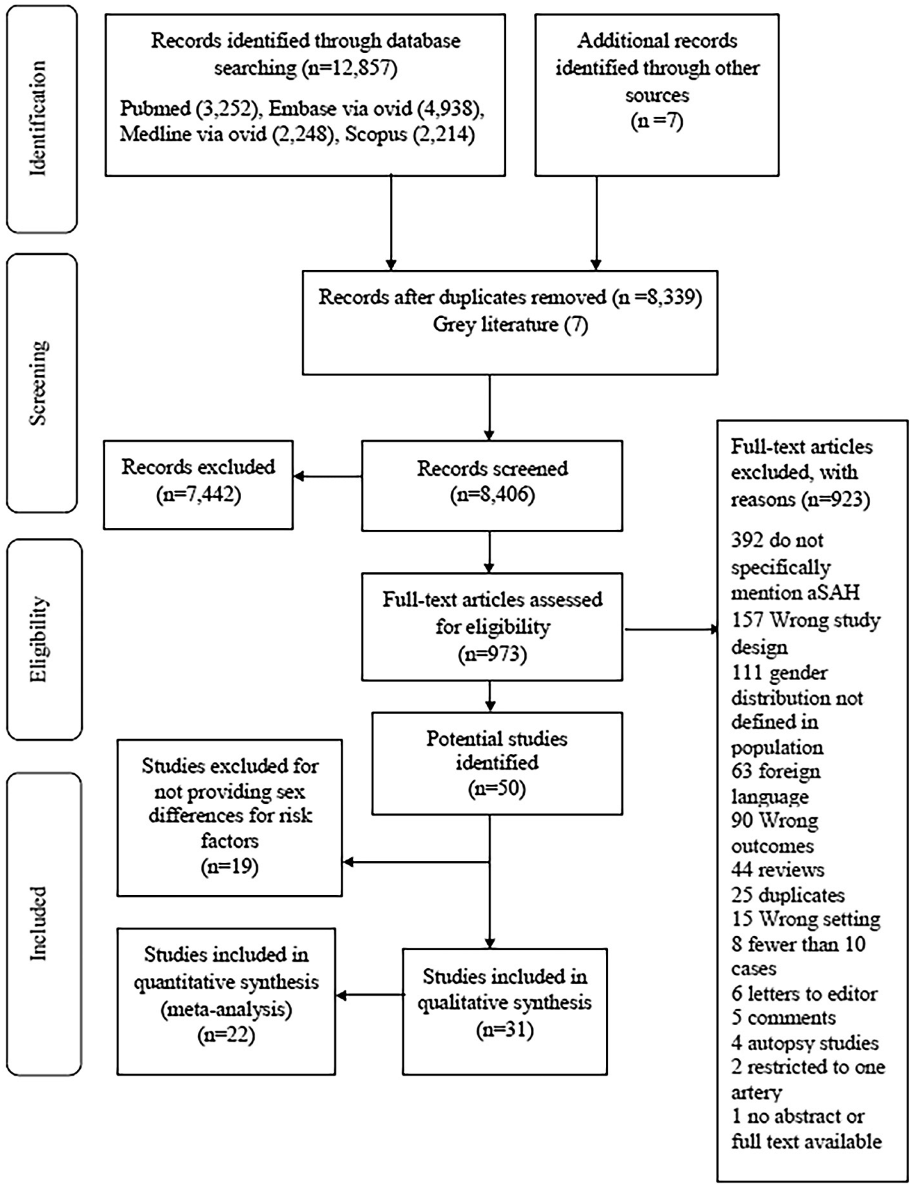

Fig 1. Prisma flow chart for the selection of the studies for systematic review and meta-analysis.

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] 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.

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.

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 (Krakow)	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
Gaist 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
Koshy 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 (Krakow)	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 & 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. [23]	1987	Sweden (Gothenburg)	1970–1979	551	SAH predilection area & marital status	Medical records
Sandvei et al. [18]	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. [12]	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.

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.

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 microanatomy 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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