Diabetes mellitus and the risk of aneurysmal subarachnoid haemorrhage: A systematic review and meta-analysis of current evidence

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Abstract

Objective: This systematic review aimed to define the relationship between diabetes mellitus (DM) and the risk of aneurysmal subarachnoid haemorrhage (aSAH).

Methods: Studies associated with DM and aSAH published until March 2016 were retrieved from Pubmed, Embase, Web of Science, and Cochrane Library databases. A random-effects model was used to calculate the relative risks (RRs) with 95% confidence intervals (CIs).

Results: Eighteen observational studies were retrieved. The overall RRs for DM and aSAH were RRs = 0.59 (0.44, 0.79), with moderate heterogeneity ($I^2 = 55.7\%$, $P_{heterogeneity} = 0.000$). Subgroup analysis by study quality revealed a reduced association between DM and aSAH risk in high quality studies only (RRs = 0.40, 95% CI: 0.29, 0.56; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.549$), therefore study quality may be a source of heterogeneity.

Conclusion: A potential decreased risk of aSAH in DM patients was found in high quality studies. Further studies are required to confirm this causal relationship and to investigate the biological mechanisms.

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Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) comprises 85% of all SAH cases.[1,2] Approximately 17,000 people in the United States are affected by aSAH each year.[3] It has been deemed a serious subtype of stroke with high fatality rate and poses a significant threat to public health.[1,4–8] Despite the recent advance in treatments and management, the poor prognosis has not been improved.[9] Effective prevention based on a better understanding of the etiology of aSAH is vital. Some researchers have reported that race, female sex, age, cigarette smoking, hypertension, heavy alcohol intake, and family history are predisposing risk factors for aSAH.[10–14]

Diabetes mellitus (DM) is the most common endocrine disorder and a major cause of disability worldwide.[15] It is calculated that the number of DM patients will increase from 246 million to 380 million over the next twenty years[16] due to burgeoning population, changed lifestyles, and population ageing.[17] DM influences the arterial wall by different mechanisms[18–20] and is a well-known trigger for cerebral infarction.[21,22]

A recent study suggested that DM was associated with a decreased risk of saccular intracranial aneurysm rupture, which may cause aSAH.[23] However, multiple epidemiologic studies have produced inconsistent and inconclusive results regarding the relationship between DM and aSAH.[10,24–40] Hence, we conducted a systematic review and meta-analysis to evaluate the current evidence from published observational studies relating to the association between DM and the risk of aSAH.

Materials and methods

We conducted this systematic review and meta-analysis in adherence to the guidelines of the Meta-analyses of Observational Studies in Epidemiology (MOOSE) group.[41]

Data sources and searches

Two investigators (X.Y. and C.J.) independently performed a systematic search of literature published until March 28, 2016 in Pubmed, Embase, Web of Science, and Cochrane Library databases. The following search terms were used: (diabetes OR diabetes mellitus) AND (intracranial aneurysm OR intracerebral aneurysm OR cerebral aneurysm OR subarachnoid haemorrhage) AND risk. No restrictions on language or types of publications were imposed. The reference lists of retrieved publications were also searched for additional relevant studies.

Study selection

Studies were included in our meta-analysis if they met the following criteria: 1) The study design was a cohort or case-control study; 2) the study described the impact of DM on the risk of aSAH; 3) the study presented odds ratios (ORs), hazard ratios (HRs), or relative risks (RRs) with corresponding 95% confidence intervals (CIs) (or sufficient data to calculate them). In instances where multiple reports were based on the same study population, we included the most informative and comprehensive studies in our systematic review.

Data extraction and methodological quality assessment

Study selection and data extraction were conducted respectively by two investigators (X.Y. and C.J.). We extracted the following information using a standardized collection form: the first author's last name, year of publication, study period, study design, number of aSAH patients and participants, source of controls, outcome data, and adjustment for major confounding factors.

The study quality of each included case-control or cohort study was assessed using the Critical Appraisal Skills Program (CASP).[42] These questions appraised

the study validity, risk of bias in recruitment, exposure and outcome measurement, confounders, the reported results, generalizability, and transferability. Each single included study was independently assessed by two reviewers (X.Y. and C.J.). Any disagreements were judged by a third investigator (G.J.) and settled by consensus.

Statistical analysis

If the prevalence of aSAH was rare, ORs and HRs were considered equal to RRs.[43] So, a RR with 95% CI was used to measure the relationship between DM and aSAH. If outcomes for males and females were provided, then risk estimates for males and females were regarded as two separate results.[44] The Cochran's Q test was used to assess the statistical heterogeneity (significant if $P < 0.10$).We employed I^2 statistics to evaluate the degree of heterogeneity among included studies.[45] We applied the random-effects model, which combined both within- and between-study heterogeneity to summarize the risk estimates.[46] Subgroup analyses were made for study design and study quality assessed by CASP. Sensitivity was analysed by omitting one study at a time to assess the stability of the pooled consequences. We examined the potential evidence of publication bias by Begg funnel plots and Egger's test.[47,48] A *P*-value of < 0.05 was regarded as statistically significant. All statistical tests were performed using STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Literature search

The electronic search yielded 1,295 potential articles. Duplicates and studies that did not meet the inclusion criteria were excluded. After this, 18 studies were chosen for detailed appraisal. Among them, one study[49] only contained an abstract; three

studies[23,50,51] were neither case-control studies nor cohort studies; four studies[52–55] did not report the association of DM with the risk of aSAH; one study[56] came from the same study population. The remaining nine studies[30–38] of interest were found by manual searching. Thus, 18 studies[10,24–40] were included in our meta-analysis. The flow chart of our searching process is shown in Figure 1.

Description of included studies

Characteristics of the included studies are presented in Table 1. Studies were published between 1991 and 2015. Six of the 18 included studies[25,26,29,30,35,39] were conducted in Japan, three[31,33,34] in the United States, two[32,36] in Australia and New Zealand, and one each in Finland,[10] Germany,[38] England,[40] the Netherlands,[37] Portugal,[24] Mexico,[27] and India.[28]Fifteen[24–38] studies were case-control studies and three[10,39,40] were cohort studies that reported the correlation between DM and the risk of aSAH. Except for one[32] study that only included female subjects, males and females were included. Various covariates were adjusted in most studies, although these differed between studies.

Only one study distinguished between type 1 and type 2 DM; this study described the association between type 2 DM and the risk of aSAH.[40] Most studies did not define DM and confirmed DM through the patient's medical history. Nevertheless, three[10,24,39] studies defined DM according to the World Health Organization's criteria, and one[27] used the definition established by the standard guidelines of the American Diabetes Association. In most studies, aSAH was diagnosed using computed tomography and/or cerebral angiography. Some studies used surgery or necropsy and cerebrospinal fluid analysis to confirm the diagnosis. A few studies[30,37,40] confirmed aSAH from the medical history. Most studies
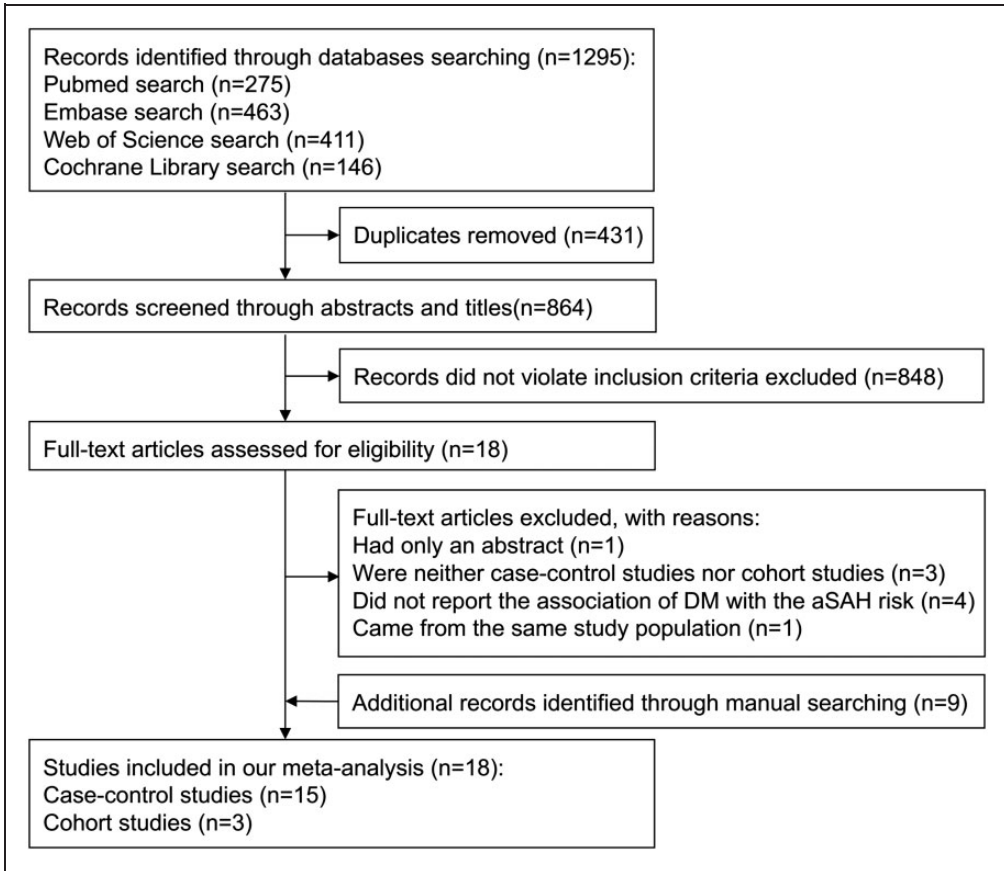
Figure 1. Flow chart of the search procedure.

reported participant satisfaction; two studies[10,38] showed < 90% satisfaction and participant satisfaction was not reported in two studies.[24,32]

Methodological quality assessment

The study quality assessment is presented in Tables 2 and 3. In total, five [26,27,29,39,40] studies were high quality and the others were poor quality. Seven[25,26,28,30,34,35,38] case-control studies recruited controls from hospitals, which was not representative of the participants. Results from two[24,35] studies contradicted other available evidence. Most studies only adjusted for age and sex.

Adjustment for other important confounders such as cigarette smoking, hypotension, alcohol consumption, body mass index (BMI), and cholesterol varied among the studies. Two[39,40] studies adjusted for the use of antihypertensive drugs. Very few studies investigating the risk of DM and aSAH adjusted for other chronic diseases, such as heart[26,29] and liver disease.[26]

Qualitative association of DM and aSAH risk

Data were available on 2,005,419 participants, including 4,327 aSAH patients. All included studies except two[24,35] reported

Table 1. Main characteristics of the included studies.

Author; year	Study period/years of follow-up	Country	Study design	Sex	No. of cases/No. of controls	RR and 95% CI (DM versus non-DM)	Adjustment
Knekt 1991	1966–1972/22	Finland	Cohort	M + F	187/42862	M: 0.7 (0.1, 4.7) F: 0 (0, 2.9)	Age
Canhao 1994	1985–1990	Portugal	Case-control	M + F	134/134	2.7 (0.9, 8.3)	None
Kunze 2000	1997–1998	Germany	Case-control	M + F	44/44	0.06 (0, 1.02)	None
Kubota 2001	NS	Japan	Case-control	M + F	127/127	0.49 (0.09, 2.74)	None
Qureshi 2001	1990–1997	United States	Case-control	M + F	323/969	0.7 (0.4, 1.2)	Age, sex, race
Mhurchu 2001	1995–1998	Australia/New Zealand	Case-control	F	268/286	0.47(0.22, 1.00)	Age, sex, city of residence
Kissela 2002	1997–2000	United States	Case-control	M + F	107/197	0.6 (0.2, 1.6)	Age, sex, race
Ohkuma 2003	1989–1998 and 2000–2001	Japan	Case-control	M + F	390/390	0.73 (0.42,1.27)	Age, sex
Broderick 2003	1994–1999	United States	Case-control	M + F	312/618	0.75 (0.41,1.38)	Age, sex, race
Inagawa 2005	1980–1998	Japan	Case-control	M + F	247/247	0.33 (0.13, 0.84)	Age, sex, hypertension, smoking, drinking, total cholesterol level, heart disease, liver disease
Okamoto 2005	1992–1997	Japan	Case-control	M + F	201/402	2.6 (1.2, 6.7)	Age, sex, family history, smoking
Sandoval 2009	2002–2004	Mexico	Case-control	M + F	231/231	0.34 (0.17, 0.68)	Age, sex, hypertension, smoking, drinking
Koshy 2010	2003–2008	India	Case-control	M + F	163/150	0.34 (0.15, 0.76)	None
Inagawa 2010	1981–2005	Japan	Case-control	M + F	798/798	0.41 (0.26, 0.64)	Age, sex, hypertension, smoking, drinking, hypercholesterolemia, heart disease
Cui 2011	NS/median 12.0	Japan	Cohort	M + F	122/35657	M: 0.15 (0.01, 2.47) F: 0.97 (0.3, 3.15)	Age, systolic blood pressure, smoking, drinking, BMI, HDL cholesterol, total cholesterol, triglycerides, antihypertensive medication, fasting status, residential areas.

(continued)

Table I. Continued.

Author, year	Study period/years of follow-up	Country	Study design	Sex	No. of cases/No. of controls	RR and 95% CI (DM versus non-DM)	Adjustment
Shiue 2012	1995–1998	Australia/New Zealand	Case-control	M + F	432/473	0.61 (0.35, 1.06)	None
Vlak 2013	2006–2009	Netherlands	Case-control	M + F	250/574	0.5 (0.2, 1.2)	Age, sex
Shah 2015	1998–2010/NS	England	Cohort	M + F	11/1921260	0.48 (0.26, 0.89)	Age, sex, systolic blood pressure, smoking, BMI, HDL cholesterol, total cholesterol, deprivation, statin and antihypertensive drugs

Abbreviations: NS, not stated; RR, risk ratio; CI, confidence interval; F, female; BMI, body mass index; HDL, high-density lipoprotein.

reduced RRs for aSAH patients with DM versus non-DM. Knekt et.al.[10] and another two[39,40] cohort studies did not show a significant reduction in the association between DM and aSAH risk with regard to sex. However, Inagawa reported a statistically inverse correlation between DM and aSAH risk in female participants, especially those who were ≥ 60 years of age.[26,29] The largest cohort study[40] from England revealed a significantly decreased association [HR, 0.48 (0.26,0.89)] between DM and aSAH risk, while other European studies gave non-significant results. Most high quality studies were from Asia[26,29,39] and these authors reported conflicting outcomes.

Synthetic association of DM and aSAH risk

RRs for the association of DM and aSAH risk were calculated in 18 studies and ranged from 0 – 2.7.[10,24–40] Overall, DM significantly reduced the risk of aSAH [0.59 (0.44, 0.79)], with substantial heterogeneity ($I^2 = 55.7\%$, $P_{heterogeneity} = 0.000$). Forest plots of the association between DM and aSAH risk are presented in Figure 2.

Subgroup analyses

Study design

The correlation between DM and aSAH was evaluated in three cohort studies and 15 case-control studies (Table 4). The summarized RR was 0.34 (95% CI: 0.09, 2.14; $I^2 = 68.4\%$, $P_{heterogeneity} = 0.013$) in the cohort studies,[10,39,40] and 0.61 (95% CI: 0.46, 0.82; $I^2 = 53.1\%$, $P_{heterogeneity} = 0.001$) in case-control studies.[24–38]

Study quality assessed by CASP

No significant connection between DM and aSAH was discovered in low and moderate quality studies[10,24,25,28,30–38] (RRs = 0.69,

Table 2. Summary of critical appraisal of case-control studies.

Criteria	Canhao 1994	Kunze 2000	Kubota 2001	Qureshi 2001	Mhurchu 2001	Kissela 2002	Ohkuma 2003	Broderick 2003
Clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y
Appropriate method?	Y	Y	Y	Y	Y	Y	Y	Y
Acceptable case recruitment?	Y	Y	Y	Y	Y	Y	Y	Y
Acceptable control recruitment?	Y	C/T	C/T	Y	Y	Y	C/T	C/T
Exposure accurately measured?	Y	Y	Y	Y	Y	Y	Y	Y
Confounders accounted for?	Y	Y	Y	Y	Y	Y	Y	Y
Confounding factors in the design and/or analysis taken account of?	N	N	N	N	N	N	N	N
What are the results?	C/T	C/T	C/T	C/T	C/T	C/T	C/T	C/T
How precise are the results?	C/T	C/T	C/T	C/T	C/T	C/T	C/T	C/T
Do you believe the results?	Y	Y	Y	Y	Y	Y	Y	Y
Applicable to the local population?	Y	Y	Y	Y	Y	Y	Y	Y
Fits with other available evidence?	N	Y	Y	Y	Y	Y	Y	Y
Do you believe the results?	Y	Y	Y	Y	Y	Y	Y	Y
Total methodological quality	L	M	M	M	M	M	M	M

Y-Yes; N-No; H-High; L-Low; M-Moderate; C/T-Cannot tell.

Table 3. Summary of critical appraisal of cohort studies.

Criteria	Knekt 1991	Cui 2011	Shah 2015
Clearly focused issue?	Y	Y	Y
Acceptable cohort recruitment?	Y	Y	Y
Exposure accurately measured?	Y	Y	Y
Outcome accurately measured?	Y	Y	Y
Important confounding factors identified?	Y	Y	Y
Confounding factors in the design and/or analysis taken into account?	N	Y	Y
Was the follow-up complete?	Y	Y	Y
Was the follow-up long enough?	Y	Y	Y
What are the results of the study?	C/T	Y	Y
How precise are the results?	C/T	C/T	Y
Do you believe the results?	Y	Y	Y
Applicable to the local population?	Y	Y	Y
Agrees with other evidence?	C/T	Y	Y
Total methodological quality	M	H	H

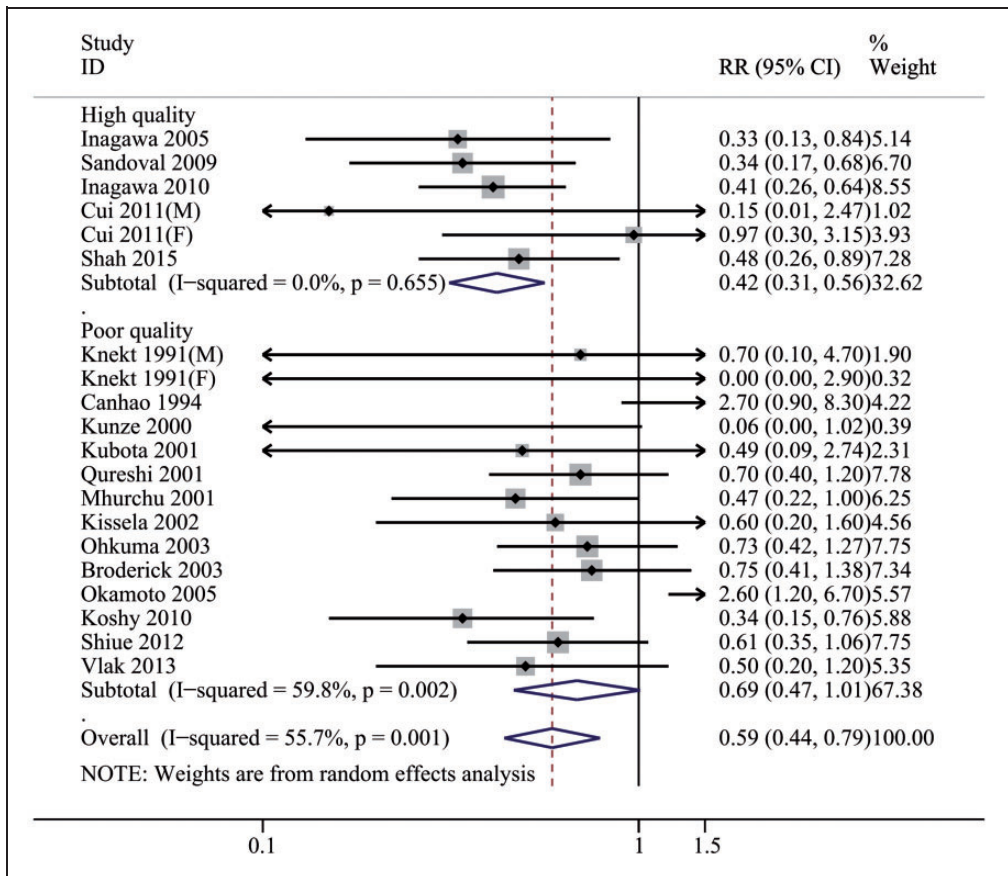Y-Yes; N-No; H-High; L-Low; M-Moderate; C/T-Cannot tell.

Figure 2. Forest plots for the risk of diabetes mellitus and aneurysmal subarachnoid hemorrhage.

Table 4. Synthetic RRs for diabetes mellitus and aneurysmal subarachnoid hemorrhage.

Subgroup	No. of studies	Synthetic estimation		Heterogeneity	
		RR (95% CI)	P-value	I^2 (%)	P-value
Total studies	18	0.59 (0.44, 0.79)	0	55.7	0.001
Study design					
Cohort	3	0.34 (0.09, 2.14)	0.103	68.4	0.013
Case-control	15	0.61 (0.46, 0.82)	0.001	53.1	0.008
Study quality					
High	5	0.38 (0.27,0.54)	0	0	0.655
Moderate and Low	13	0.69 (0.47,1.01)	0.056	59.8	0.002

Abbreviations: RR, relative risk; CI, confidence interval; BMI, body mass index.

95% CI: 0.47, 1.01; $I^2 = 58.3\%$, $P_{heterogeneity} = 0.002$), whereas a statistically significant correlation was found in high quality studies[26,27,29,39,40] (RRs = 0.40, 95% CI: 0.29, 0.56; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.549$) (Figure 2, Table 4).

Sensitivity analysis and publication bias

Outcomes were stable except for one study (Figure 3). No evidence of meaningful publication bias was indicated by the Begg funnel plot (Figure 4) and Egger's test ($P_{Egger} = 0.396$).

Discussion

The incidence of cerebrovascular disease is 1.7 times higher in diabetic patients than non-diabetic persons.[57] The cerebrovascular complications of DM are restricted to atherosclerotic disease and cerebral infarction, and the frequency of cerebral infarction is higher than expected in diabetic patients.[58,59] However, the Harvard Cooperative Stroke Registry reported a low occurrence of DM in patients with aSAH.[60] To date, the contribution of DM to the development of aSAH remains unclear. In our systematic review, all included studies except for two[24,35] reported a decreased association between DM and aSAH risk. This meta-analysis using RRs from 15 case-control studies and three cohort studies included more than 2,000,000 individuals, therefore our findings indicate that DM reduces the risk of aSAH.
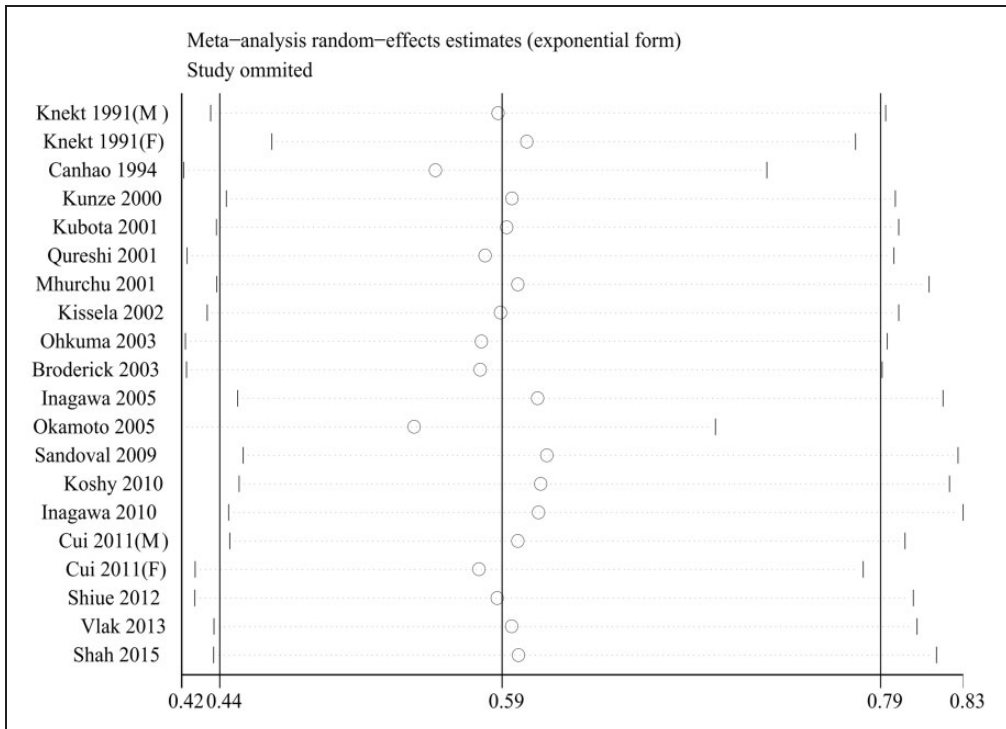

Figure 3. Sensitivity analyses for the risk of diabetes mellitus and aneurysmal subarachnoid hemorrhage.
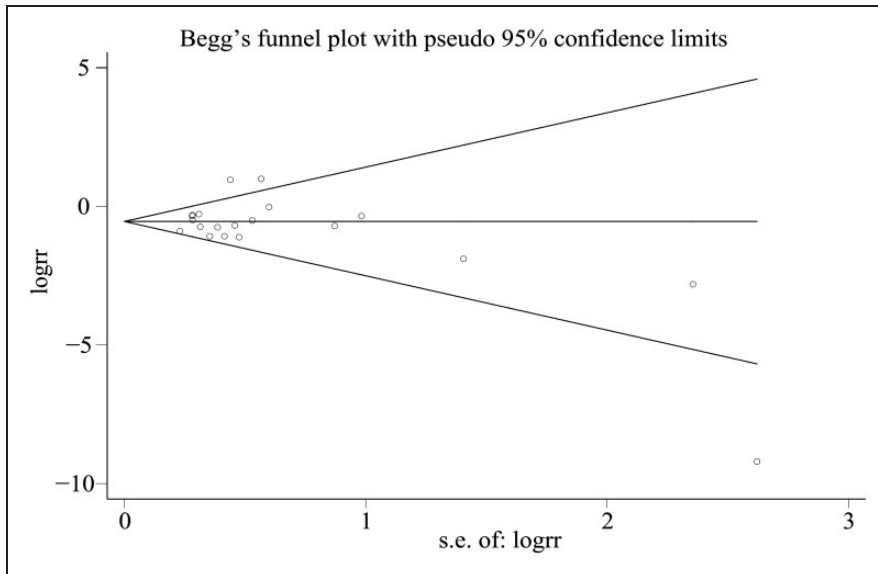
Figure 4. Begg funnel plot for the risk of diabetes mellitus and aneurysmal subarachnoid hemorrhage.

Strengths and limitations of this systematic review

To the best of our knowledge, this is the first systematic review and meta-analysis to focus on the association between DM and risk of aSAH. All available published studies with a sufficient number of participants for a qualitative and quantitative summary of the outcomes were included in this meta-analysis. Therefore, this study has more power than any individual study to investigate the relationship between DM and risk of aSAH.

Substantive heterogeneity between studies was monitored using the I^2 statistic. The findings of observational studies should always be interpreted with caution. Subgroup analysis by study design showed that the majority of included studies were case-control studies, therefore our conclusions are chiefly based on case-control studies. Diabetic patients probably have a higher risk of dying from other diseases than non-diabetic individuals. Consequently, the likelihood of a SAH forming is reduced in DM patients compared with controls.[57] At the same time, recall and selective bias may be increased.

The most important limitation highlighted by the current systematic review was the paucity of high quality studies. Only half of the included studies were of high quality. Insufficient study quality may be a source of heterogeneity according to the subgroup analysis of study quality. The CASP clearly demonstrated that recruited controls were unrepresentative, identified a large number of unadjusted potential confounders, and showed that unprecise results are the main cause of poor study quality. Because the study quality was limited and the heterogeneity was moderate, it was not possible to show a stronger association for population characteristics, such as geographical areas and sex.

Study quality may have been a contributing factor to heterogeneity, but there were other potential sources. For example, only a few studies[10,27,39] specifically defined DM. The lack of a consistent standard definition

for DM may have affected the number of diabetic patients recruited in each study. Similarly, some studies[30,39,40] did not describe the methods of aSAH diagnosis, which may also have contributed to heterogeneity.

Prospective population-based cohort studies have shown that BMI and cholesterol levels may be related to DM and may protect against aSAH.[10,61,62] Information about important risk factors such as BMI[39,40] and cholesterol levels[26,39,40] were only collected in a few studies. Other important risk factors such as cigarette smoking, hypotension, and alcohol consumption were generally inconsistent among the included studies. These factors have been associated with an increased risk of aSAH,[10–14] but very few studies adjusted for them. This may explain the unprecise findings regarding risk of aSAH among the included studies.

Because the collected information was limited, we could not distinguish between type 1 and type 2 DM. This might have prevented identification of a genuine association between DM and risk of aSAH. For example, in type 1 diabetic patients, the prevalence of nonaneurysmal SAH was high in a prospective cohort study.[55] Because the quality of the included studies was generally poor, we did not calculate the RR and 95% CI to detect more sources of heterogeneity, such as the methods for measuring diabetes, antidiabetic drugs, and duration of diabetes in each study. Notably, antidiabetic drugs were used by 9% of type 2 diabetic patients in a comparative study, but was not related to the risk of aSAH according to multivariate analysis.

We did not perform an exhaustive search of the published literature in all electronic databases; therefore we may have missed several pertinent published or unpublished studies. Finally, we found little proof of publication bias in our meta-analysis. However, potential publication bias might

have had an impact on our findings, as statistical tests have shown.[47,48]

Comparison with previous studies

Feigin et al. performed a meta-analysis[63] to evaluate various SAH risk factors published before 2005. Surprisingly, they found that DM was associated with a reduced risk of SAH [RR, 0.3 (0 to 2.2) including one[10] longitudinal study [OR, 0.7 (0.5 to 0.8)] and six[25,30,31,33,38,56] case-control studies]. However, the sample size and study quality were questionable in this study. The sample size and study quality [25,27,29,39,40] were better in the present meta-analysis [RR, 0.38 (0.27, 0.54)]. Our study yielded a narrower 95% CI of pooled aSAH RR associated with DM compared with the earlier meta-analysis, indicating that our results are more precise.

Only two of the included studies reported an increased association between DM and the risk of aSAH, largely because of small sample sizes and univariate analysis. If an increased association between DM and aSAH is confirmed by future studies, then special determination assessment will be affected, including cerebral angiography of patients with DM and recent symptoms of third nerve palsy.[64]

Hypothetical causes for the reduction of DM and aSAH risk

Although there are no confirmed biological theories to support our finding, several putative explanations exist. Patients with DM may modify their lifestyles (e.g., more exercise, better diet, less smoking and drinking) and receive medication for hypertension, which is an independent risk factor of aSAH.[64] Inagawa suggested that an inverse association exists between DM and aneurysm rupture, which might be linked to the atherosclerotic wall because atherosclerotic aneurysms are less likely to rupture.[29] This might also explain why the decreased

association is stronger in older diabetic patients than younger diabetic patients.[29] Similar to saccharification of the extracellular matrix and cross-linking between elastin and avitene in the aortic wall,[65] diabetes-mediated alterations might exist in the hemal extracellular matrix.[40] Furthermore, the 9p21.3 locus has been related to DM and saccular IAs,[66,67] although it is not part of the linkage disequilibrium block. A genetic connection that enhances type 2 DM and reduces the risk of aSAH is likely to exist.[23]

Implication for future research

Future studies will need to be well-designed and carefully powered to address the following points: (1) consideration of more potential confounding factors, such as BMI, cholesterol level, smoking, hypertension, and drinking; (2) adjustment for or exclusion of chronic diseases (heart disease was associated with a decreased risk of aSAH, possibly due to reduced strenuous physical activity); (3) investigation of possible therapeutic mechanisms; (4) classification of DM as type 1 and type 2 to determine a potential causal relationship.

Conclusions and unanswered questions

In conclusion, most of the studies included in our systematic review are lacking in quality. Analysis of the high quality studies identified a potential decreased risk of aSAH in subjects with DM. However, the causal relationship between DM and aSAH remains to be elucidated. Further high quality epidemiological cohort and animal studies are necessary to investigate whether DM and aSAH are correlated and to elucidate the underlying biological mechanisms.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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