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Diabetes, hypertension, smoking, and hyperlipidemia as risk factors for spontaneous cervical artery dissection: Meta-analysis of case-control studies

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Keywords
Vertebral Artery Dissection; Carotid Arteries; Hypertension; Smoking; Diabetes Mellitus

Abstract

Background: Spontaneous cervical artery dissection (sCeAD) is an important cause of ischemic stroke in the young population and has a different cardiovascular risk profile from other causes of ischemic stroke. No study provided a comprehensive evidence for cardiovascular risk factors of sCeAD.

Methods: We searched PubMed, MEDLINE, and Embase without date or language restrictions for relevant studies. Bibliographies of included studies were also searched. We included case-control studies where patients with sCeAD were on one arm, and controls were on the other arm. The investigated risk factors were diabetes, hypertension, smoking, and hyperlipidemia. Data extraction and quality assessment were performed independently by two reviewers.

Results: Seventeen qualifying case-control studies were identified, comparing 2185 patients with sCeAD and 3185 healthy control subjects. Heterogeneity was low for diabetes, moderate for hypertension and hyperlipidemia, and high for smoking. The meta-analysis showed a significant association between hypertension and sCeAD [pooled odds ratio (OR) = 1.70, 95% confidence interval (CI): 1.40-2.07, P < 0.001]. There was no association between sCeAD and diabetes (pooled OR = 0.71, 95% CI: 0.50-1.01, P = 0.060) or smoking (pooled OR = 0.90, 95% CI: 0.68-1.20, P = 0.480). Hyperlipidemia was negatively-associated with sCeAD (OR = 0.65, 95% CI: 0.48-0.89, P = 0.007), but with sensitivity analysis, there was no association (OR = 0.72, 95% CI: 0.44-1.19, P = 0.200).

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Conclusion: The meta-analysis reveals that sCeAD has a significant association with hypertension and no association with smoking, diabetes, or hyperlipidemia. These results should direct future research towards exploring biological mechanism of hypertension-induced arterial dissection.

Introduction

Globally, 13 million people develop a new stroke annually,[1] with 10% of these occurring in people between 18 to 50 years of age.[2] About 13% of ischemic stroke in the young population is related to cervical artery dissection (CeAD), including carotid artery dissection (CAD) and vertebral artery dissection (VAD).[3] Sixty-one percent of CeAD is spontaneous (sCeAD), occurring without trauma.[4] Many studies investigated the etiology and risk factors of sCeAD, and identified numerous genetic and environmental factors including α1-antitrypsin deficiency,[5] hyperhomocystinemia,[6-8] recent infection,[9,10] styloid process length[11-13] or its proximity to the hyoid bone,[14] arterial tortuosity,[15-17] and connective tissue disorders.[18,19] However, cardiovascular risk factors such as smoking, hypertension, and diabetes were less investigated. The multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study suggests that patients with sCeAD are more frequently hypertensive and more likely to suffer from obesity and hypercholesterolemia than their sex and age-matched controls.[20] Pezzini et al. specifically investigated the association of traditional cardiovascular risk factors with pathogenesis of sCeAD in a case-control study and found a positive association with hypertension. They also reported statistically insignificant association with diabetes, smoking, and hypercholesterolemia.[21]

We conducted this meta-analysis to identify the association between cardiovascular risk factors including hypertension, diabetes, smoking, and hyperlipidemia by comparing patients with sCeAD and controls of patients with no evidence of sCeAD or ischemic stroke. As there is uncertainty of the association of traditional cardiovascular risk factors with sCeAD due to the small number and size of case-control studies, we aimed to explore this association in a meta-analysis to generate bigger numbers that could reliably compare sCeAD with healthy population.

Materials and Methods

This study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[22]

Eligibility criteria: In this review, we included case-control studies where patients with any combination of sCeAD, CAD, or VAD were on one arm, and controls were on the other arm, regardless of study objectives. The studies reported odds ratio (OR) and confidence interval (CI) for cardiovascular variables or provided figures where these statistical measures could be executed. We excluded cohort studies that had no control group, randomized controlled trials (RCTs) that normally adjusted for cardiovascular risk factors and were less likely to compare sCeAD with a healthy control group, and studies that had less than 10 patients on the case group to reduce small study size bias. If the same author group used the same data on more than one qualifying study, the study with the biggest number on the sCeAD arm was selected, or otherwise, the most recent study. In addition, we excluded any study that did not report at least one of the three cardiovascular variables of interest for the purpose of this study, and any study that compared sCeAD with other ischemic stroke patients. We accepted any definition of hypertension or diabetes (whether self-reported or measured), but only history of current smoking was included.

Search strategy: Two independent investigators conducted literature search on three databases including PubMed Central, MEDLINE, and Embase for eligible studies, with no language restriction. The combinations of search terms used for Ovid Embase included ('cervical artery' OR 'carotid artery' OR 'vertebral artery') AND ('dissection' OR artery dissection') AND ('smoking' OR 'hypertension' OR 'diabetes mellitus'). Their equivalent terms were used for the other two databases, with omission of the terms related to cardiovascular risk factors for PubMed Central to broaden the search. The full details of the search strategy for the three databases are provided in supplementary file.

Search of all databases was done from their inception to November 10, 2020. The reference list of all retrieved articles was also searched for any additional eligible studies. Abstracts of the identified articles were then examined for eligibility by the two reviewers in parallel and examining the full text was carried out if required due to uncertainty. Any discrepancy between the two reviewers and disagreements was resolved by consensus or input of the senior author.

Data collection: Screening of the abstract or the full text of all the selected studies was performed to confirm eligibility. Then the duplicate references were identified and excluded. Data extraction and quality assessment were performed independently by the two independent reviewers, and any disagreements were resolved as described above. Data that were extracted from included articles included: publication information, characteristics of the study population, statistical measures, and data to measure risk of bias.

Risk of bias assessment between individual studies: Two separate authors used the Newcastle-Ottawa Scale (NOS) for case-control studies[23] to assess for the risk of bias within individual studies. Studies were allocated stars based on the following domains: 1) adequacy of case definition, representativeness of cases and selection and definition of controls, 2) comparability of cases and controls on the basis of the design or analysis, 3) method and comparability of exposure ascertainment for cases and controls and description of non-response rate. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars can be given for comparability. A maximum of 9 stars could be allocated to each study, and we took a cut-off of 6 or less as an indicator of high risk of bias.

Assessment of publications bias: We used visual assessment of funnel plot asymmetry for assessment of publication and other potential bias. Funnel plot was generated by plotting the standard error (SE) of log OR against OR. Presence of publication bias was also assessed with Egger's test, and if this was significant, we used the non-parametric Duval and Tweedie's trim and fill, where missing studies were imputed to the right of the mean to provide a true effect estimate.

Review Manager (RevMan) 5.4.1 software was used to calculate estimate effects, generate forest plots, and conduct sensitivity analysis. Generation of funnel plot and assessment of its asymmetry, Egger's regression test, trim and fill, and meta-regression of diabetes log OR on sCeAD and control age were performed with Comprehensive Meta-Analysis (CMA) software version 3.3.070. We treated the four cardiovascular variables as dichotomous outcomes and calculated their pooled OR and 95% CI. Heterogeneity between studies was quantified using both χ^2-based Cochran's Q-test with a $P < 0.01$ taken as significant, and I^2-statistic with a cut-off value of > 50% as a measure of significant inconsistency. Random effects model was used for analysis for all cardiovascular variables irrespective of heterogeneity. We also used sensitivity and subgroup analysis to investigate for heterogeneity. Sensitivity analysis was performed with sequential elimination of studies one by one, elimination of studies with a sample size of < 100 on the cases arm, and elimination of studies with a high risk of bias, which was a score of less than seven out of nine on the NOS.

Results

Study selection: The search of all three databases resulted in 3103 records, and two more eligible studies were identified via examining the reference list of selected studies. After elimination of duplicates and review of titles and abstracts, 61 titles remained suitable for further assessment for eligibility. Forty-four studies were excluded, and 20 studies remained that fulfilled the selection criteria apart from use of same data by same first authors or same author group. We selected one of three studies by Pezzini et al, which was the most recent and had the biggest number of patients in the sCeAD arm.[21] Two more studies were from the CADISP group and had two different first authors, from which the most recent study was selected which also had the biggest number of patients in the sCeAD arm. That resulted in 17 studies[8,16,17,20,21,24-35] to be included in the qualitative and quantitative synthesis (including studies cited in tables 1 and 2). Figure 1 shows PRISMA study flow diagram.

All selected studies were published in English. Only three studies were focused on cardiovascular risk factors as the main objective. Seventeen studies reported on smoking and hypertension, while data on diabetes were obtained from 14 studies. The included studies compared 2184 patients with sCeAD and 3185 healthy control subjects. Tables 1 and 2 show baseline characteristics of included studies. There was no significant difference in age between sCeAD and control groups (standard difference in means = 0.01, P = 0.810).

Risk of bias within individual studies: The risk of bias of individual studies using the NOS ranged from 5 to 9, with 16 out of 17 studies scoring 6 to 9 and 10 out of 17 studies scoring 7 to 9. The full scoring table is provided in supplementary files.

Cardiovascular risk factors for sCeAD: Smoking showed no statistical association with sCeAD (pooled OR = 0.90, 95% CI: 0.68-1.20, P = 0.480) (Figure 2).

Table 1. Characteristics of 17 case-control studies included in the meta-analysis

Author	Country	Setting	Patients with sCeAD (N)	Control group (N)	Patient selection	Control selection	Study comparison	Dissected vessel	NOS bias scale
Arauz et al.[8]	Mexico	Hospital (tertiary referral center)	39	76	sCeAD on MRA	Relatives and friends with non-vascular neurological disorders	Homocysteine, B12, and folate levels and MTHFR polymorphism	ICA and VA	6
Arnold et al.[24]	France	Hospital	239	516	Cervical MRI and MRA or DSA	Healthy persons undergoing systematic health examinations	Vascular risk factors	ICA and VA	6
Artto et al.[25]	Finland	Hospital (tertiary referral center)	313	313	All fulfilling selection criteria	Finnish population register center	Migraine with aura	ICA and VA	8
Debette et al.[20]	CADISP	International multicenter	690	1170	Prospective and retrospective registry	Existing population-based surveys	Vascular risk factors	ICA and VA	7
D'Anglejan-Chatillon et al.[26]	France	Hospital	50	100	Retrospective records	Spouses and friends	Migraine	ICA and VA	7
Gallai et al.[27]	Italy	Hospital	26	30	Consecutive sCeAD	Outpatient headache clinic	Homocysteine and MTHFR polymorphism	ICA and VA	7
Genius et al.[28]	Germany	Hospital	21	54	Consecutive sCeAD	Population registries	C-reactive protein	ICA and VA	9
Giossi et al.[16]	Italy	Hospital	102	102	Consecutive sCeAD	Patients hospitalized for non-stoke causes	Arterial tortuosity	ICA and VA	6
Guillon et al.[29]	France	Hospital	47	52	Consecutive sCeAD	Hospital staff	Hemodynamic and morphologic properties of the carotid artery	ICA	7
Hori et al.[30]	Japan	Hospital	43	63	Consecutive sCeAD	Outpatients with headache	Anatomical variations of vertebra-basilar artery	Vertebro-basilar	6
Kim et al.[17]	South Korea	Hospital	75	75	Consecutive sCeAD	People undergoing routine health check-up	Arterial tortuosity	ICA and VA	5
Kim et al.[31]	USA	Hospital	83	83	Consecutive sCeAD	Patients with negative CTA and no stroke	Arterial tortuosity	ICA	7
Konrad et al.[32]	Germany	Hospital	95	95	Consecutive sCeAD	Population-based study on cardiovascular risk factors	Homocysteine, B12, and folate levels and MTHFR polymorphism	ICA and VA	7
Longoni et al.[33]	Germany	Hospital	96	204	Consecutive sCeAD, 2 groups	Healthy volunteers from population registries	ICAM-1 E469K gene polymorphism	ICA and VA	8
Pezzini et al.[21]	Italy	National multicenter	153	153	Consecutive	List of local general practitioners by random digit dialing	Arterial hypertension	ICA and VA	8

Table 1. Characteristics of 17 case-control studies included in the meta-analysis (continue)

Author	Country	Setting	Patients with sCeAD (N)	Control group (N)	Patient selection	Control selection	Study comparison	Dissected vessel	NOS bias scale
Ruiz-Franco et al.[34]	Mexico	Hospital	100	100	Consecutive	Unrelated healthy volunteers from blood bank	TGFBR2 mutation and MTHFR-C677T polymorphism	Cervico-cerebral	8
Strege et al.[35]	Germany	Hospital	34	25	Consecutive sVAD	Stroke mimics	Contributing factors to quality of life	VA	8

CADISP: Cervical Artery Dissection and Ischemic Stroke Patients (an international multicenter study); MRI: Magnetic resonance imaging; MRA: Magnetic resonance angiography; DSA: Digital subtraction angiography; CTA: Computed tomography angiography; sCeAD: Spontaneous cervical artery dissection; ICA: Internal carotid artery; VA: Vertebral artery; MTHFR: Methylenetetrahydrofolate reductase; sVAD: Spontaneous vertebral artery dissection; ICAM-1: Intercellular adhesion molecule-1; NOS = Newcastle-Ottawa Scale

Table 2. Characteristics of 17 case-control studies included in the meta-analysis

Author	Patients' age (mean ± SD)	Controls' age (mean ± SD)	Women/men in sCeAD group	Women/men in control group	Ascertainment of dissection	FMD in patients' group [n (%)]	FMD in control group [n (%)]
Arauz et al.[8]	39.3 ± 11.5	37.2 ± 9.6	20/19	38/38	MRA or conventional angiography	NG	NG
Arnold et al.[24]	44.4 ± 9.4	44.4 ± 9.7	119/120	263/263	MRA or DSA	NG	NG
Artto et al.[25]	46.1 ± ??	45.8 ± ??	105/208	105/208	CTA	NG	NG
Debette et al.[20]	44.2 ± 9.9	45.9 ± 8.1	303/387	516/654	CTA or MRA	NG	NG
D'Anglejan-Chatillon et al.[26]	NG	NG	25/25	50/50	CTA	NG	NG
Gallai et al.[27]	51.6 ± 15.4	50.6 ± 11.5	11/15	15/15	MRA or conventional angiography	7 (27.0)	0 (0)
Genius et al.[28]	40.5 ± 8.2	39.4 ± 7.7	10/11	24/30	MRA	NG	NG
Giossi et al.[16]	44.7 ± 7.8	43.4 ± 7.5	35/67	35/67	MRA or conventional angiography	NG	NG
Guillon et al.[29]	49.7 ± 8.0	47.5 ± 8.0	9/17	9/17	MRA or conventional angiography	NG	NG
Hori et al.[30]	49.2 ± 11.0	50.5 ± 10.3	19/24	29/34	MRA and (CTA or DSA)	NG	NG
Kim et al.[17]	44.6 ± 12.9	44.6 ± 12.9	16/59	16/59	CTA or MRA	NG	NG
Kim et al.[31]	49.2 ± 10.6	49.5 ± 10.7	38/45	38/45	CTA	9 (11.0)	7 (8.4)
Konrad et al.[32]	42.6 ± 10.2	44.5 ± 8.5	37/58	37/58	MRA or DSA	NG	NG
Longoni et al.[33]	41.7 ± 7.5	39.4 ± 9.3	58/38	113/91	DSA +/- MRA	NG	NG
Pezzini et al.[21]	45.2 ± 13.1	44.5 ± 12.9	67/86	67/86	MRA or conventional angiography	NG	NG
Ruiz-Franco et al.[34]	38.1 ± 10.7	38.1 ± 10.6	35/65	35/65	CTA, MRA and/or DSA	NG	NG
Strege et al.[35]	62.6 ± 11.9	62.4 ± 10.7	10/24	16/22	CTA or MRA	NG	NG

MRA: Magnetic resonance angiography; DSA: Digital subtraction angiography; CTA: Computed tomography angiography; sCeAD: Spontaneous cervical artery dissection; FMD: Fibromuscular dysplasia; NG: Not given; SD: Standard deviation

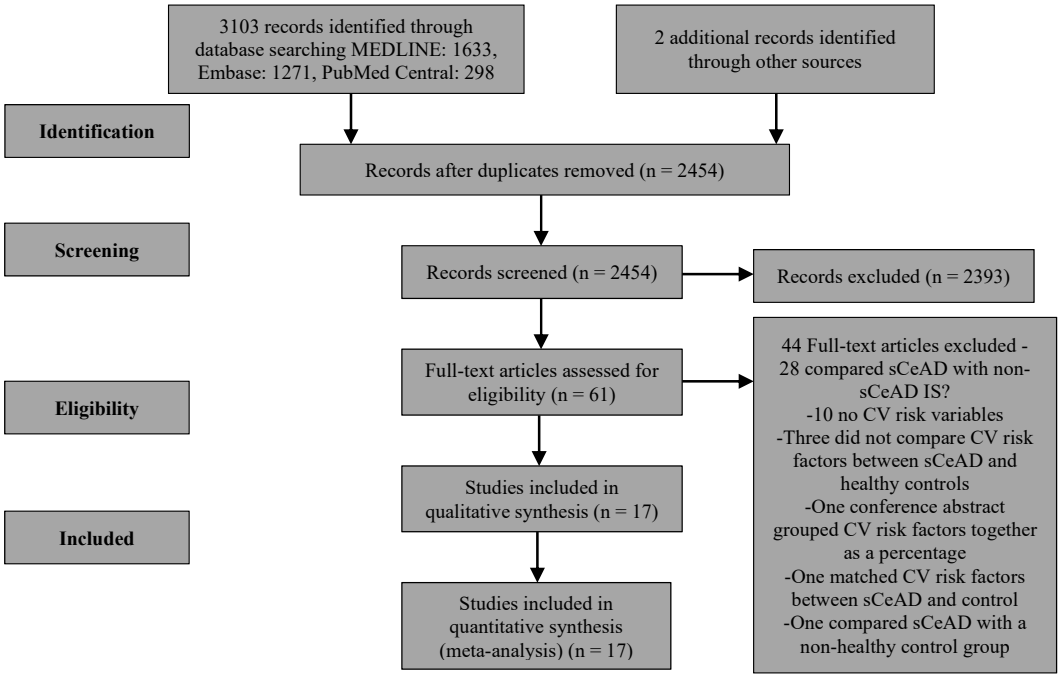

Figure 1. PRISMA study flow diagram
sCeAD: Spontaneous cervical artery dissection; CV: Cardiovascular; IS: Ischemic Stroke

This result did not change with sensitivity analysis performed with sequential elimination of studies one by one and by elimination of all studies with a case number size of < 100 (OR = 1.26, 95% CI: 0.88-1.80) or elimination of studies with high risk of bias (OR = 0.78, 95% CI: 0.52-1.16). Sensitivity analysis did not identify the source of heterogeneity.

In this meta-analysis, we identified a strong association between hypertension and sCeAD (pooled OR = 1.70, 95% CI: 1.40-2.07, P < 0.001) (Figure 3). This statistical association remained significant after sensitivity analysis done by elimination of individual studies one by one, elimination of studies with a case number smaller than 100 (OR = 1.66, 95% CI: 1.30-2.12), and elimination of studies with high risk of bias (OR = 1.74, 95% CI: 1.37-2.23).

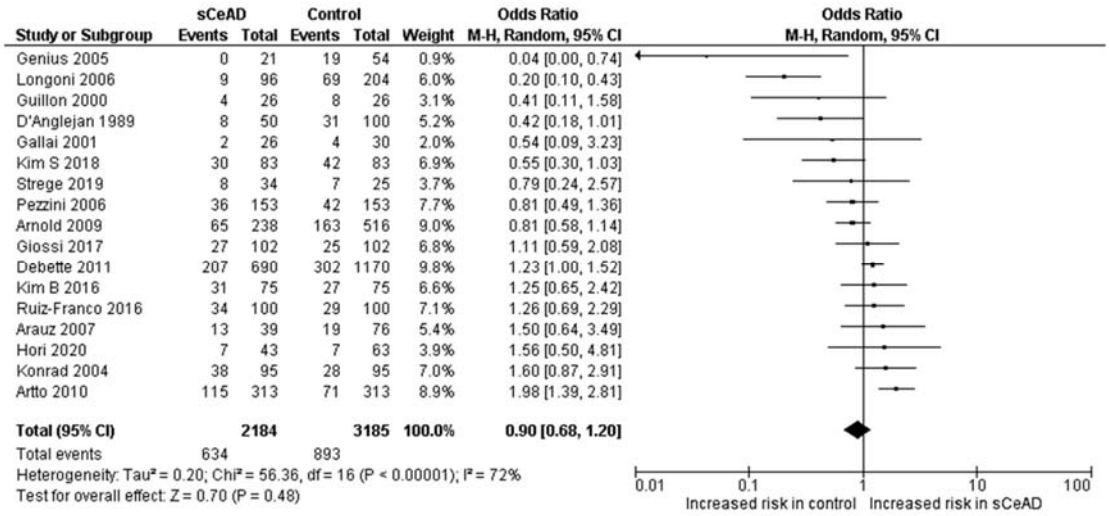

Figure 2. Forest plot of 17 studies showing no significant association between smoking and spontaneous cervical artery dissection (sCeAD)

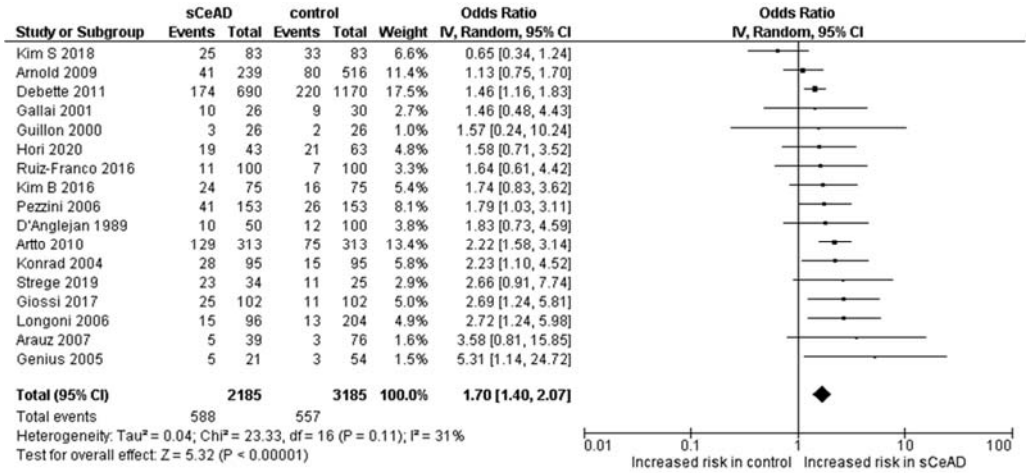

Figure 3. Forest plot of 17 studies showing significant association between hypertension and spontaneous cervical artery dissection (sCeAD)

Diabetes showed no association with sCeAD (pooled OR = 0.71, 95% CI: 0.50-1.01, P = 0.060) (Figure 4) and there was no association after performing sensitivity analysis, using sequential elimination of individual studies. The single study by Debette et al.[20] had the most significant effect on results, as elimination of this study from analysis resulted in a pooled OR of 0.79 and 95% CI of 0.54-1.17 (P = 0.250). Further sensitivity analysis with elimination of studies with high risk of bias also showed no statistical significance (pooled OR: 0.66, 95% CI: 0.42-1.03, P = 0.070). However, subgroup analysis of studies with a case number > 100 showed borderline significance (OR = 0.68, 95% CI: 0.45-1.01, P = 0.050). The absence of significant association between diabetes and sCeAD was not affected by mean age.

Eight studies reported on frequency of hyperlipidemia in the sCeAD and control groups with variable definitions and ascertainment of hyperlipidemia as shown in supplementary file. Only one study (Arnold et al.[24]) reported numerical figures of hyperlipidemia, and the rest of studies presented it as a dichotomous variable. As shown in forest plot (Figure 5), hyperlipidemia was negatively-associated with sCeAD (OR = 0.65, 95% CI: 0.48-0.89, P = 0.007). However; sensitivity analysis with inclusion of studies that only compared total cholesterol between the sCeAD and control groups showed no statistical association (OR = 0.72, 95% CI: 0.44-1.19, P = 0.200).

The included studies showed a variable heterogeneity for the different cardiovascular risk factors, being high for smoking (I^2 = 72%), modest for hyperlipidemia (I^2 = 54%), and low for hypertension and diabetes (I^2 = 37% and I^2 = 9%, respectively).

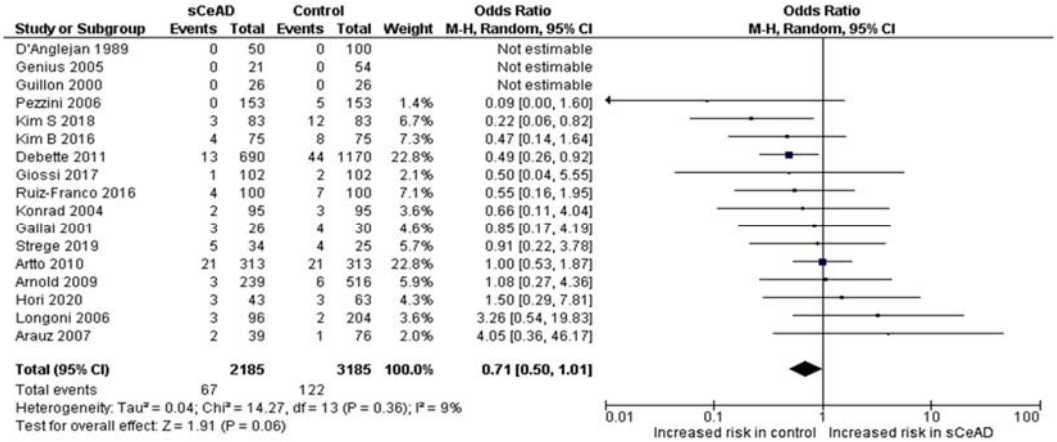

Figure 4. Forest plot of 14 studies showing significant association between diabetes and spontaneous cervical artery dissection (sCeAD)

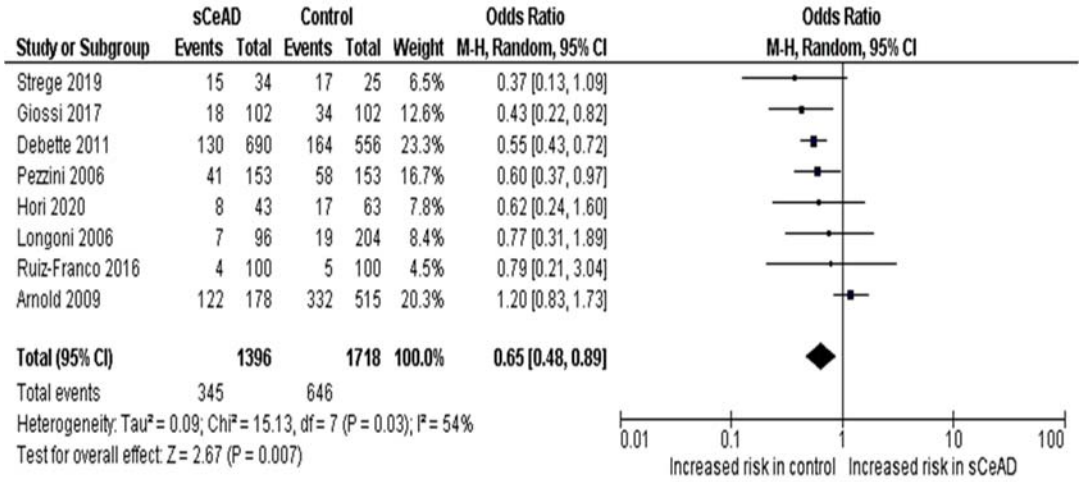

Figure 5. Forest plot of 8 studies showing significant association between hyperlipidemia and spontaneous cervical artery dissection (sCeAD)

Visual assessment of funnel plot for the smoking variable of included studies showed minor asymmetry. This was further verified with Egger's regression test, which was significant (P = 0.029). Subsequently, Duval and Tweedie's trim and fill method was performed to explore for missing studies to the right of the mean. Four studies were imputed, and the overall effect estimate changed from 1.046 to 1.098 (Figure 6).

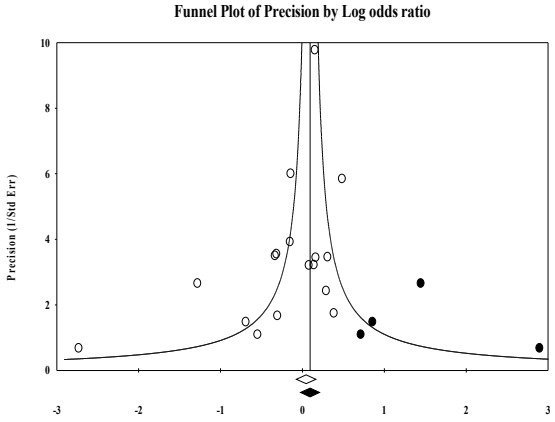

Figure 6. Funnel plot showing minor asymmetry. Each white dot represents a single study from the original dataset, and black dots represent imputed missing studies to reflect a true estimate effect in the absence of publication bias. The vertical line is the line of significance and the diagonal lines represent standard error, within which 95% of studies lie in the absence of publication bias or heterogeneity. The white diamond represents the pooled estimate effect from meta-analysis, and the black diamond represents the true estimate effect.

Discussion

To our knowledge, this is the first meta-analysis of cardiovascular risk factors of sCeAD. We showed no significant association between smoking and sCeAD that was not altered by sensitivity analysis. Moreover, the meta-analysis of all included studies initially showed no negative association between diabetes and sCeAD though P-value was borderline (0.06). However, this lack of association was more evident with sensitivity analysis. The study by Debette et al. had the most biased estimate effect.[20] It is an international multicenter study with significant heterogeneity in the methods of control selection and risk factor evaluation. In addition, the prevalence of diabetes in both cases and controls was low (2.9% and 4%, respectively), making this factor of less importance. The mean age of patients across most of the included case-control studies was 40 to 50 years, and the prevalence of diabetes in the same age group in 2010 in Germany (where many of the case-control studies of this meta-analysis were conducted) was 1.6% for men and 1.3% for women.[36] This further suggests that the initial results were related to control selection bias. There was also a significant association between sCeAD and hypertension, and this association remained significant with all sensitivity analyses, eliminating small study size effect and selection and selective reporting bias. This association was shown in two of the three case-control studies that specifically addressed cardiovascular risk factors of sCeAD. The authors of this meta-analysis could not give a certain explanation for this association.

However, it is possibly related to elevated shear stress across the vascular lumen induced by fluctuations in blood pressure as occurs in aortic dissection.[37] This usually results in dissection in the presence of pre-existing cystic medial necrosis, which is also more prevalent in hypertensive subjects, and increases progressively with age.[38] This was demonstrated experimentally by injecting water into post-mortem aortas, and the required pressure to induce dissection reduced significantly with age.[39] Many studies suggest that hypertension is the most important risk factor for aortic dissection though the mechanism of association is not clear.[40-42] This mechanism is probably different from cervical artery dissection, as aortic dissection affects older people with more prevalence of atherosclerosis than in patients with sCeAD.[43] The absence of association of sCeAD with diabetes and smoking and the negative association with obesity and hypercholesterolemia[20] suggest that the effect of hypertension on sCeAD is mechanical rather than atherosclerotic. Hypertension could possibly lead to dissection of a cervical artery that suffers from weakness or stiffness from other multiple genetic and environmental factors. This remains as an association but not causation. Animal models could possibly be used to identify the mechanical effects of hypertension on cervical arterial wall.[44,45] Another possible link between sCeAD and hypertension is fibromuscular dysplasia (FMD). This condition may account for up to 15% of cases of sCeAD.[46] In about 75% of cases,[47,48] it involves the renal arteries leading to renal artery stenosis, which is a recognized cause of renovascular hypertension in the young population.[49] Therefore, both hypertension and sCeAD could represent different manifestations of FMD. In our review, only two studies[27,31] presented data on imaging below the neck to support the diagnosis of FMD. The prevalence of FMD in the two studies was 14.7% and 6.2% in sCeAD and control groups, respectively.

This meta-analysis initially showed negative association between sCeAD and hyperlipidemia, but the number of studies that compared serum lipids in sCeAD and control patients was small, and they reported on different combinations of lipids with different methods of ascertainment. Sensitivity analysis of studies that only compared total cholesterol between sCeAD and healthy control groups showed no association. The association between sCeAD and hyperlipidemia requires further case-control studies and meta-analysis for more meaningful conclusions.

The lack of association between smoking and sCeAD is not generalizable due to significant unexplained heterogeneity between studies. The same applies to the doubtful association between diabetes and sCeAD due to small number of events in cases and controls and low prevalence of diabetes in this age group. Bigger case-control studies in the future and incorporation of those studies in a meta-analysis in a decade or so may consolidate these results. The positive association between hypertension and sCeAD, on the other hand, is likely generalizable, though the explanation is only theoretical and further case-control studies and meta-analysis might also confirm this association.

Conclusion

This meta-analysis showed that hypertension had a significant association with the development of sCeAD, diabetes had a tendency towards a negative effect that was more likely related to individual study bias, and smoking and hyperlipidemia had no effect. We take the association of sCeAD with smoking, hyperlipidemia, and diabetes with caution, but the association with hypertension is possibly generalizable though it needs further research. Further studies should explore the biological mechanism of the effects of hypertension on cervical vessel wall.

Limitations: This meta-analysis is the first study to pool data of cardiovascular risk factors from case-control studies comparing sCeAD with controls. Due to small numbers of individual studies, this meta-analysis provides bigger numbers for more meaningful effect estimates. We performed a robust literature search, with no language restriction. However, there are many limitations of this analysis. First, there is significant heterogeneity for the smoking outcome, which was explored but no source was identified. Second, the heterogeneous characteristics of healthy controls across included studies (relatives, subjects from headache clinics, hospital staff, stroke mimics, etc.) make it difficult to reliably compare studies, but on the other hand, could be regarded as a strength of the analysis. Third, the risk factor definition and evaluation varied between studies. While some studies used objective measurement of blood pressure, others relied on patients' personal history or use of antihypertensive medications.

Last, we treated both CAD and VAD as one entity. Cardiovascular risk factors could have more influence on one or the other.

Conflict of Interests

The authors declare no conflict of interest in this study.

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