Association between primary Sjögren's syndrome, cardiovascular and cerebrovascular disease: a systematic review and meta-analysis

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ABSTRACT

Objective. *Acute systemic inflammation and chronic systemic vasculitis are associated with endothelial dysfunction and atherosclerotic plaque formation. Studies on cardiovascular or cerebrovascular events in primary Sjögren's syndrome (pSS) are limited, with conflicting results. This meta-analysis aimed to explore the risk of cardiovascular and cerebrovascular disease in pSS.*

Methods. *A comprehensive search of the MEDLINE and EMBASE databases was performed from date of inception through August 2017. The inclusion criterion was observational studies evaluating the association between pSS and cardiovascular disease or cerebrovascular event. Outcomes are diagnosis of ischaemic heart disease, myocardial infarction, ischaemic stroke or haemorrhagic stroke. The pooled odds ratio (OR) of the cerebrovascular event or cardiovascular disease and their 95% confidence interval (CI) were calculated using a random-effect meta-analysis to compare risk between patients with pSS and controls. The between-study heterogeneity of effect-size was quantified using the* Q *statistic and* I^2.

Results. *Data were extracted from 10 observational studies involving 165,291 subjects. Pooled result demonstrated a significant increase in risk of having cardiovascular disease or cerebrovascular event in pSS patients compared with controls (OR=1.28; 95% CI: 0.11-1.46, p value<0.01, I^2=68%). Subgroup analyses showed no difference in risk for cerebrovascular event (OR=1.31; 95% CI: 0.96-1.79, p value=0.09, I^2=71%), but an increased risk of cardiovascular disease (OR=1.30; 95% CI: 1.09-1.55, p value=0.003, I^2=74%).*

Conclusion. *Our study has shown an increased risk of cardiovascular or cerebrovascular disease in patients with pSS. These results support the findings of multiple studies of increased arterial stiffness in patients with pSS.*

Introduction

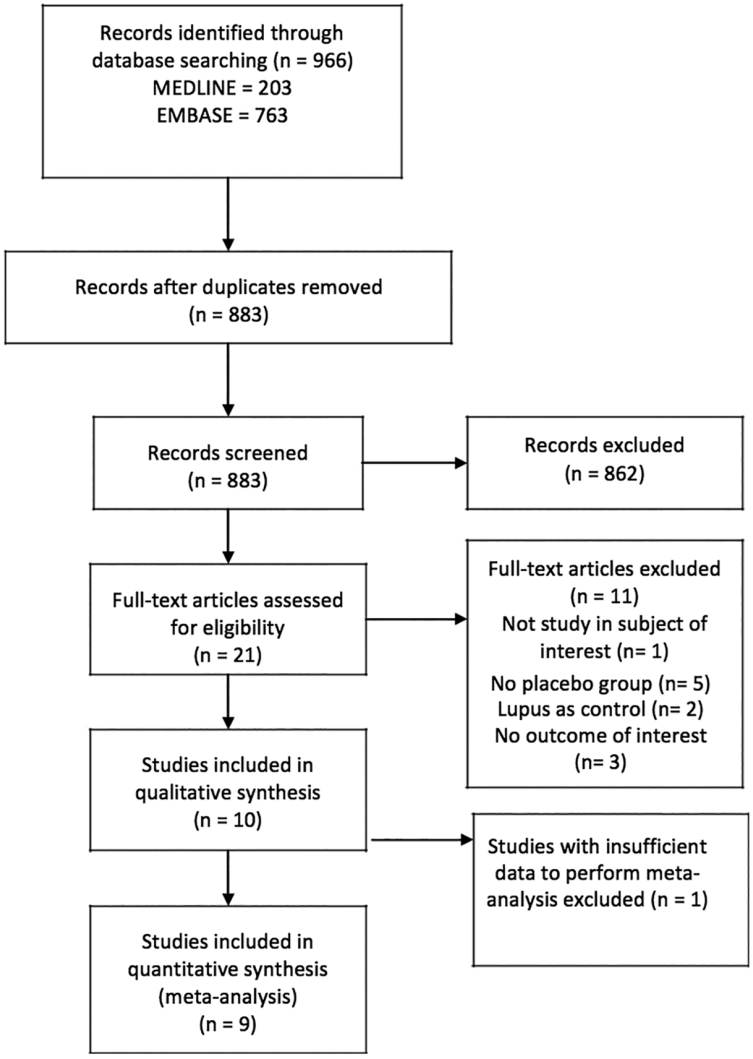
Sjögren's syndrome is one of the most common rheumatic diseases that affect females, especially in their fourth decade of life, with a prevalence rate of 0.1-4.8% of the total female population. It is characterised by lymphocytic infiltration of the lacrimal and salivary glands, causing keratoconjunctivitis sicca and xerostomia, which are the most common manifestations of this disease (1). Sjögren's syndrome can present either as primary Sjögren's syndrome (pSS) or secondary to other underlying connective tissue diseases, most commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). There is at least one-third of patients with pSS could present with extra-glandular involvement; these include thyroid, lungs, GI, vasculitis, renal, haematological, central and peripheral nervous system. Cardiovascular involvement in pSS is less commonly seen. Rare complications such as acute pericarditis and myocarditis were reported (2), but thus far the well-known cardiac involvement of pSS is the association of anti-SSA with congenital heart block, which is one of the manifestations of neonatal lupus. On the contrary, heart block is rare in adults and not consistently associated with anti-SSA (3). Another well-studied association is the increased risk of ischaemic stroke in pSS secondary to antiphospholipid syndrome (APS).

Several studies have demonstrated that acute systemic inflammation and chronic systemic vasculitis are known to be associated with endothelial dys-

function (4). In certain rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), the tendency to atherosclerosis is a major cause of mortality (5), but the studies of atherosclerosis in pSS have been inconclusive. Necrotising vasculitis of medium-sized vessels resembling polyarteritis nodosa can occur in patients with Sjögren's syndrome (6). The association of chronic systemic vasculitis in pSS and atherosclerosis is unclear. There have been few studies that evaluated subclinical atherosclerosis by measuring the pulse wave velocity or carotid artery intima-media thickness, concluded that pSS might have a higher frequency of subclinical atherosclerosis (7-10). Few other studies have evaluated the relationship between pSS and the risk of subsequent stroke in pSS with a mixed result, depending on sex and other comorbidities (11-13). Other studies have suggested patients with pSS may associate with increased prevalence of hyperlipidaemia (14), hypertriglyceridaemia (15), and less diabetes mellitus (16).

Apart from that, studies on cardiovascular or cerebrovascular event in pSS are few and conflicting. Therefore we conduct this meta-analysis to explore the risk of cardiovascular and cerebrovascular event in pSS, namely ischaemic heart disease, myocardial infarction, ischaemic stroke or haemorrhagic stroke.

Fig. 1.



Materials and methods

This systematic review and meta-analysis was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement (17) and was registered in PROSPERO (registration number: CRD 42017057275).

Search strategy

Three authors (WCY, AS, SU) independently searched published studies indexed in MEDLINE and EMBASE from date of inception to August 2017. References of all selected studies were also examined. The following main search terms were used: Sjögren's syndrome, coronary artery disease, acute coronary syndrome, myocardial infarction, angina, ischaemic heart disease, cerebrovascular accident, cerebral infarction, and stroke. The full search terms used are detailed in the Supplemental material and methods.

Inclusion and exclusion criteria

This review included all published observational studies including cross-sectional, prospective cohort, retrospective cohort and case-control studies that assessed the association of primary Sjögren's syndrome, cardiovascular and cerebrovascular disease. Reviews, case reports, and abstracts were excluded because their quality of studies could not be assessed.

We included studies that recruited participants from the general population or used data from medical records from healthcare facilities. Participants were adults with primary Sjögren's syndrome or healthy individuals. We compared outcomes between patients who were diagnosed with primary Sjögren's syndrome by using the 1993 European Community Study Group diagnostic criteria (18), American College of Rheumatology criteria (19), or American-European Consensus criteria (20) and participants who did not have primary Sjögren's syndrome. Secondary Sjögren's syndrome was excluded from our study. The main outcome of this study was a diagnosis of ischaemic heart disease, myocardial infarction, ischaemic stroke or haemorrhagic stroke. The odds ratios (OR), relative risks (RR), hazard ratios (HR) or number of participants with outcome were extracted.

Data extraction

All authors independently reviewed titles and abstracts of all citations that were identified. After abstracts were reviewed, data comparisons between

Table I. Characteristics of the ten observational studies included in this review.

Study, year	Design	Study duration	Source	Country	Participants (N)	Demographics			Diagnosis criteria of disease methods	Outcome measurement and controls	Possible confounder between patients	Quality assessment (Newcastle-Ottawa Scale)
						Age		Women				
						P	C					
Kang and Lin, 2010 [14]	Case-control study	2006 –2007	National Health Insurance Research Dataset	Taiwan	1974 patients and 9870 controls	49.7±21	49.7±21	76.2%	Features of dryness of the eyes and mouth and blood antibody (such as ANA). Inclusion was based on ICD-9.	IHD, CHF, stroke	Adjusted for age, sex, urbanisation level, and monthly income only; Conditional regression analyses showed PSS patients have higher rate of HLD, hypothyroidism, liver disease but not DM or renal failure.	Selection = 3 Comparability =2 Exposure = 1
Chiang *et al*., 2013 [12]	Retrospective cohort study	Jan, 2000 – Dec 2006	National Health Insurance Research Dataset	Taiwan	5025 patients and 5025 controls	53.2±14.1	53.0±14.1	87%	American-European Consensus Group for PSS	AMI	Adjusted for age, gender. Matched for age, sex, HTN, DM, HLD, CKD, COPD; higher rate of PAD and valvular heart disease in PSS group.	Selection = 3 Comparability =2 Outcome = 3
Chiang *et al*., 2014 [11]	Retrospective cohort study	Jan, 2000 – Dec 2006	National Health Insurance Research Dataset	Taiwan	4276 patients and 42760 controls	51.2±13.7	51.2±13.7	88.4%	American-European Consensus Group for PSS	Ischaemic stroke	Adjusted for age and gender. Matched for age, sex, HTN, DM, HLD, CKD, and COPD.	Selection = 3 Comparability =2 Outcome = 3
Bartoloni *et al*., 2015 [16]	Retrospective cohort study	Not reported	Five Italian rheumatology centres for patient group; Italian 'Progetto Cuore' registry for control.	Italy	788 patients and 4774 controls	56±10	55±11	100%	1993 European Community Study Group diagnostic criteria, American-European Consensus Group for PSS	CHF, cerebrovascular events, AMI	Matched for age and sex. Higher rate of HTN, hypercholesterolaemia; lower rate of smoking, obesity, and DM in PSS group.	Selection = 2 Comparability =1 Outcome = 3
Ramagopalan *et al*., 2013 [24]	Retrospective cohort study	Jan 1999 – Dec 2011	English national Hospital Episode Statistics dataset	England	17741 patients and 7.6 million controls	Not reported	Not reported	89% vs 48%	Not reported. Inclusion was based on ICD-10 code.	SAH	Adjusted for sex, age in 5-year bands, time-period in single calendar years, region of residence, and deprivation score associated with patients' local authority area of residence in quintiles	Selection = 3 Comparability =2 Outcome = 2

Zoller *et al.*, 2012 [13]	Cohort study	Jan 1987 – Dec 2008	Several national Swedish data registers	Sweden	1300 patients. Control number not reported	Not reported	Not reported	Not reported	Not reported. Inclusion was based on ICD-7, ICD-8, ICD-9 and ICD-10 code.	Ischaemic stroke and haemorrhagic stroke	Adjusted for age, period, socioeconomic status, region of residence, hospitalisation of chronic lower respiratory diseases, obesity, alcoholism, HTN, DM, Afib, CHF, renal disease, sepsis, and CHD.	Selection = 3 Comparability =2 Outcome = 3
Chang *et al.*, 2016 [25]	Retrospective cohort study	2000 -2011	National Health Insurance Research Dataset	Taiwan	4560 patients and 18240 controls	53.9±14.1	53.8±14.2	86.5% vs 86.5%	Diagnosis based on findings of haematology and pathology report. Inclusion was based on ICD-9	Risk of GERD as primary outcome. Prevalence of IHD described in demographics	Matched for age, sex, HTN, DM; Higher rate of HLD and renal disease in PSS group.	Selection = 4 Comparability =1 Outcome = 3
Pasoto *et al.*, 2012 [26]	Cohort study	Aug 2010 - Aug 2011	Sjogren's syndrome outpatient clinic, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo	Brazil	100 patients and 89 controls	47.6±10.8	47.1±10.8	97% vs 96.6%	American-European Consensus Group for PSS	Thrombotic event (stroke, AMI, DVT)	Matched for age, sex, and ethnicity; All PSS patients with stroke had positive aPL.	Selection = 3 Comparability =1 Outcome = 2
Perez-De-Lis *et al.*, 2010 [27]	Case-control study	1984 - 2009	Autoimmune department, Hospital clinic, Barcelona	Spain	312 patients and 312 controls	Not reported	Not reported	Not-reported	1993 European Community Study Group diagnostic criteria, and American-European Consensus Group for PSS	Stroke and IHD	Matched for age and sex. Higher rate of DM and hypertriglyceridaemia; lower rate of HTN and smoking in PSS group.	Selection = 4 Comparability =1 Exposure = 2
Yeh *et al.*, 2016 [28]	Case-control study	2000 - 2011	National Health Insurance Research Dataset	Taiwan	9629 patients and 38516 controls	55 (median)	Not reported	87% vs 87%	American-European Consensus Group for PSS. Inclusion was based on ICD-9	Risk of Sjogren's syndrome in HCV and HBV hepatitis as primary outcome. Prevalence and OR of IHD as secondary outcome.	adjusted for age, sex, geographic region, occupation, monthly income, HLD, cancer, renal disease, COPD, and liver cirrhosis	Selection = 3 Comparability =1 Exposure = 2

CHF: Congestive heart failure; SAH: subarachnoid haemorrhage; GERD: gastroesophageal reflux disease; IHD: ischaemic heart disease; OR: odd ratio; HTN: hypertension; HLD: hyperlipidaemia; DM: diabetes mellitus; aPL: antiphospholipid; PAD: peripheral artery disease; CHD: coronary heart disease.

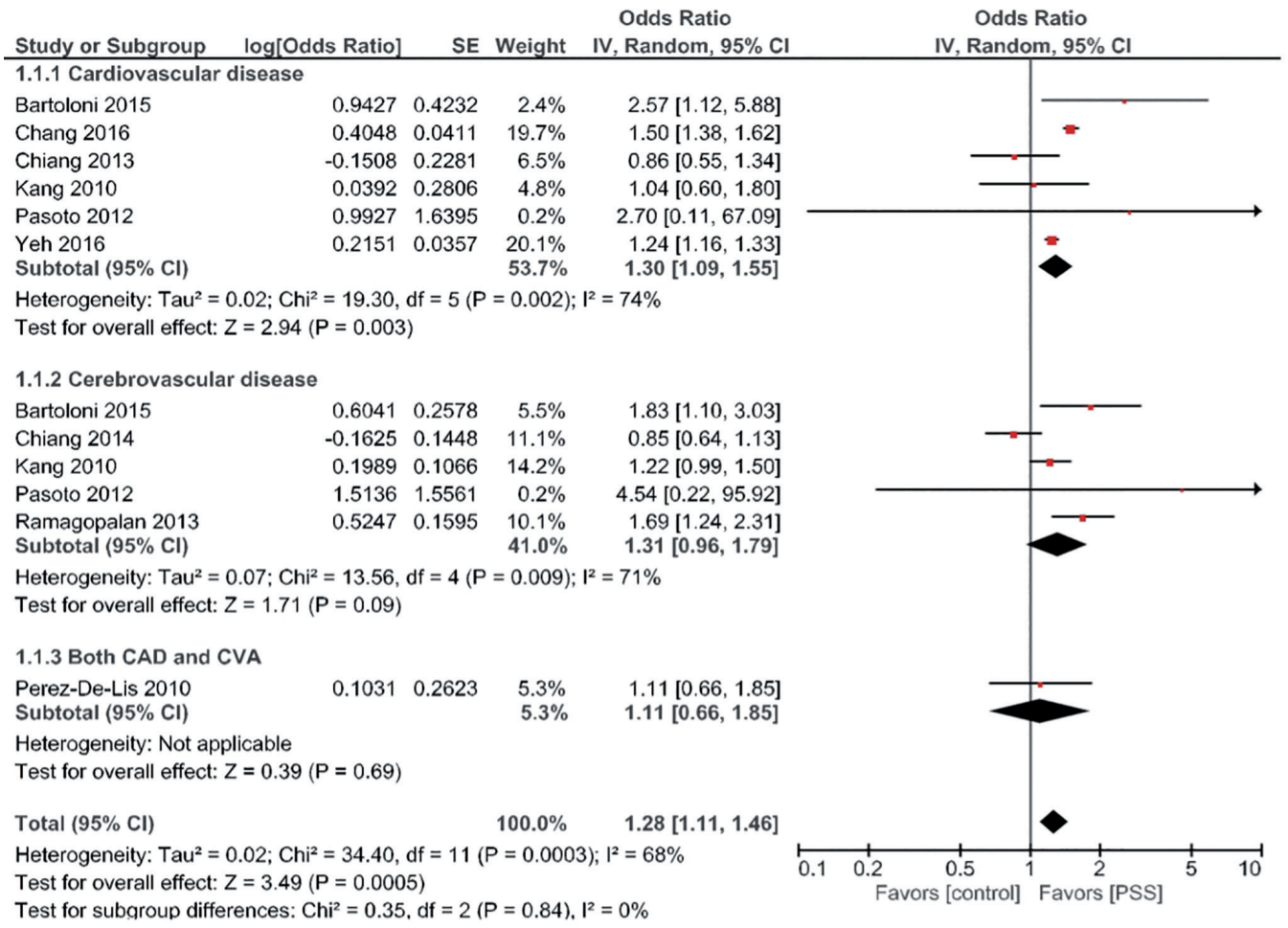


Fig. 2. Forest plot assessing the risk of cardiovascular and cerebrovascular disease in patients with and without primary Sjögren's syndrome. CI: confidence interval.

the three investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus.

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. Data concerning study design, the source of information, participant characteristics, Sjögren's syndrome and assessment of cardiovascular or cerebrovascular disease were independently extracted. We contacted the authors of the original reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

Assessment of bias risk

A subjective assessment of methodological quality of observational studies was evaluated by all three authors using the Newcastle-Ottawa Scale (NOS) (21), which is a quality assessment tool for non-randomised studies. It uses a "star system" based on three major perspectives: the selection of the study groups (0–4 stars, or 0–5 stars for cross-sectional studies), the comparability of the groups by controlling for important and additional relevant factors (0–2 stars), and the ascertainment of outcome of interest or exposure (0–3 stars). A total score of 3 or less was considered poor, 4–6 was considered moderate, and 7–10 was deemed high quality. We excluded studies from our meta-analysis if they had poor quality. Discrepant opinions between authors were resolved by consensus.

Statistical analysis

We performed a meta-analysis of the included studies using Review Manager 5.3 software from The Cochrane Collaboration to generate forest plot and funnel plot and Comprehensive Meta-Analysis 3.3 software from Biostat, Inc to perform Egger's regression test. We calculated pooled effect estimate of incidence or prevalence of cardiovascular or cerebrovascular disease with 95% confidence interval (CI) comparing between primary Sjögren's syndrome and normal groups using a random-effects model. We used effect size (OR, HR, RR) from univariate or, if available, multivariate models with confounding factors (age and gender) adjusted in each study. We excluded studies from meta-analysis and only presented the result with narrative description (qualitative analysis) when there were not sufficient data available for calculating pooled effect size. The heterogeneity of effect estimates across these studies was quantified using the Q statistic and I^2 (p<0.10 was considered statistically

significant). The Q statistic compared the observed between-study dispersion and expected dispersion of the effect size, and was expressed in *p*-value for statistical significance. An I^2 is the ratio of true heterogeneity to total observed variation. An I^2 of 0% to 40% was considered to exclude heterogeneity, of 30% to 60% was considered to represent moderate heterogeneity, of 50% to 90% was considered to represent substantial heterogeneity, and of 75% to 100% was considered to represent considerable heterogeneity (22). Publication bias was assessed using funnel plot and Egger's regression test (23).

Results

Description of included studies

The initial search yielded 883 articles (Fig. 1); 862 articles were excluded based on the title and abstract review. A total of 21 articles underwent full-length review. Eleven articles were excluded (1 article did not study the subject of interest; 5 articles had no control group; 2 articles used lupus as control group, and 3 articles did not report the outcome of interest). Data were extracted from 10 studies involving a total of 165,291 participants for qualitative analysis (11-14, 16, 24-28). The included studies varied in study location, sample size, and source of data. One study (13) was excluded from the meta-analysis because it reported the standardised incidence ratio (SIR) as outcome measurement. Among nine eligible studies that were included in the meta-analysis, three studies (14, 16, 26) reported both cardiovascular and cerebrovascular disease as outcome; five studies reported either coronary artery disease (28), ischaemic heart disease (25), acute myocardial infarction (12), ischaemic stroke (11) or subarachnoid haemorrhage (24). Lastly, one study (27) reported a combined risk of cardiovascular and cerebrovascular events. The characteristics of the ten extracted studies included in this review were outlined in Table I.

Meta-analysis results

The pooled result demonstrated a significant increase in overall risk of having cardiovascular disease or cerebrovascular event in patients who have PSS compared with controls (OR=1.28; 95% CI: 0.11-1.46, *p*-value<0.01, I^2=68%). Subgroup analyses showed no difference in risk for cerebrovascular event (OR=1.31; 95% CI: 0.96-1.79, *p*-value=0.09, I^2=71%), but an increased risk of cardiovascular disease (OR=1.30; 95% CI: 1.09-1.55, *p*-value=0.003, I^2=74%) (Fig. 2).

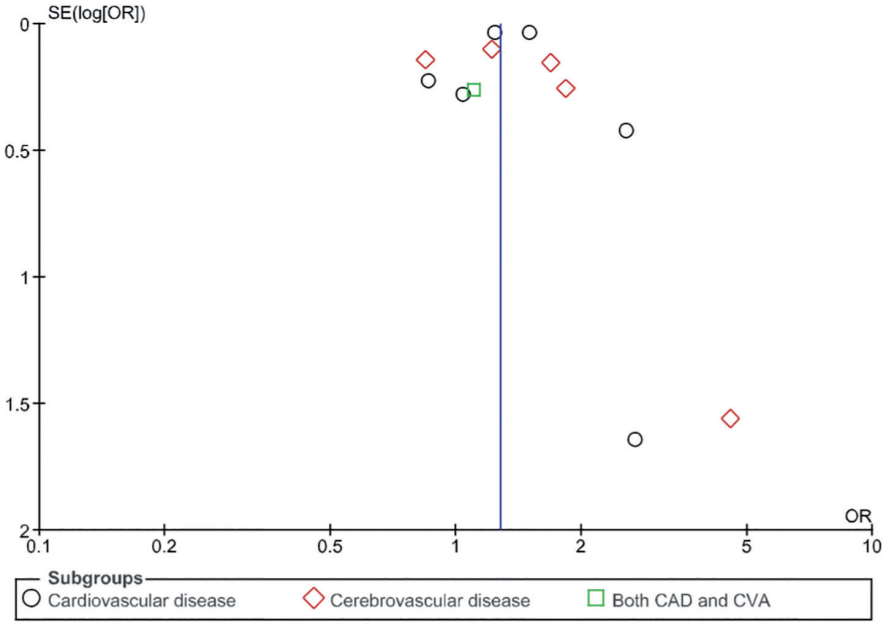


Fig. 3. Funnel plots showing studies reporting cardiovascular and cerebrovascular disease in patients with and without primary Sjögren's syndrome.

Publication bias

To investigate potential publication bias, we examined the funnel plot of the included studies in the meta-analysis of the cardiovascular and cerebrovascular disease (Fig. 3). The vertical axis represents study size (standard error) while the horizontal axis represents the difference in means. From this plot, publication bias does not exist because there is an asymmetrical distribution of studies but the Egger's test result was not statistically significant (*p*=0.47).

Discussion

To the best of our knowledge, this is the first meta-analysis to explore the association between pSS and cardiovascular or cerebrovascular event. Our systematic review and meta-analysis found that pSS is associated with increased overall risk of cardiovascular or cerebrovascular event based on the included studies to date. However, in subgroup analysis, the risk of cardiovascular disease is significantly increased in patients with pSS meanwhile there is no greater risk of cerebrovascular event in the patient group compared to control group. As aforementioned, pSS is associated with vasculitis which may increase the risk of haemorrhagic stroke because of the inflammatory infiltrates in the vascular wall. Thus Ramagopalan's study (24) was included in our meta-analysis. Despite the inclusion of this study, we have not found any increased risk of ischaemic or haemorrhagic stroke overall. A nationwide follow-up study from Sweden (13) which was not included in our study because of different outcome measurement has reported an increased risk of ischaemic stroke but not haemorrhagic stroke. This result was contradictory to Ramagopalan's study that reported an increased risk of subarachnoid haemorrhage in PSS. Noteworthily, Pasoto *et al*. (26) found that patients with PSS having a stroke are associated with positive antiphospholipid antibody but not in those having a myocardial infarction.

Our study result supports multiple studies that have reported an association between pSS and subclinical atherosclerosis by measuring carotid

intima media thickness, aortic distensibility, and pulse wave velocity (7-10). Although there is no increased risk of ischeamic or haemorrhagic stroke, the overall elevated risk of cardio- and cerebrovascular event has alerted us to manage pSS as one of the atherosclerosis risk factors, in the same manner of treating RA and SLE because atherosclerosis in RA and SLE are known to be a cause of mortality and morbidity. Studies reported that a high level of cytokines and proinflammatory markers including asymmetric dimethylarginine (ADMA) (7), soluble thrombomodulin, anti-endothelial cell antibody (AECA) (9), adhesion molecules (VCAM-1 and ICAM-1) (29) probably are contributing to the high risk of cardiovascular event in patients with pSS. The endothelial dysfunction with the increased expression of these markers and cytokines, in addition to the impairment of flow-mediated dilatation, may cause vascular fibrosis and smooth muscle cell proliferation, eventually leading to arterial stiffness and atherosclerosis. (30)

It was found that pSS also has a higher prevalence of traditional risk factors include hypertension and hyperlipidaemia but not smoking, obesity and diabetes (16). The reason of fewer smokers in pSS probably is because it causes more oral mucosa dryness and discomfort. On the contrary, Kang and Lin (14) did not find a significantly higher prevalence of hypertension, diabetes, yet a significantly higher prevalence of hyperlipidaemia in pSS. Meanwhile, Perez-De-Lis *et al*. (27) reported a two-fold higher prevalence of diabetes mellitus and 1.5-fold higher prevalence of hypertriglyceridaemia, and a lower frequency of hypertension and smoking. Several other factors may also play a role in atherosclerosis in pSS such as menopause causing female patients the loss of their hormonal cardiovascular protective effect since pSS is more commonly occurred in women in their fifties (30). Symptoms such as fatigue and depression may also lead to poor quality of life and more prone to a sedentary lifestyle, which also one of the cardiovascular risk factors.

There are few limitations of our study. First of all, all the included studies had not reported the duration of disease as we know the longer the disease duration, theoretically the more significant atherosclerotic plaque formation over time and may cause more significant disease. Another limitation as mentioned in Chiang's study (11, 12) was that patients' information such as smoking, body mass index, dietary habits, and family history of cardiovascular disease, was not available for analysis in their large population-based dataset. It also does not contain autoantibody data, and authors were unable to evaluate the severity of pSS in patients. The authors (11, 12) also stated they did not investigate the effect of medications used for pSS that might reduce the acute myocardial infarction or ischaemic stroke, and thereby our study also is unable to explore the effect of treatment on the risk of cardiovascular or cerebrovascular disease. Both of Chiang's studies enrolled control subjects that were matched with the presence of comorbid disorders including hypertension, diabetes, hyperlipidaemia, chronic kidney disease, atrial fibrillation and chronic obstructive pulmonary disease (COPD); while the remaining studies did not. Furthermore, we could not tell the occurrence of ischaemic heart disease or cerebrovascular disease in relation to the time of PSS diagnosis in certain studies (25, 28). It may bias our study result because Yeh *et al*. (28) and Chang *et al*. (25) did not report the exclusion of pSS patients with a history of cardio- or cerebrovascular event before the diagnosis of pSS, while most of the studies had described the exclusion of such a patient group (11-14, 24).

Conclusion

In conclusion, our study has shown an increased risk of overall cardio- and cerebrovascular events, especially cardiovascular disease. Few cardiovascular risk factors are more prevalent in pSS than the general population. Controlling those cardiovascular risk factors could potentially help improving their general health and avoiding both cardiovascular and cerebrovascular diseases.

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