Original Article

Periodontal conditions in patients with Sjögren's syndrome: A meta-analysis

Shih-Yun Wu [a,b], Ching-Yi Wu [c,a*], Ming-Han Chen [d,e], Hsin-Yi Huang [f], Yu-hsuan Chen [a], Yen-Po Tsao [g,e], Yu-Lin Lai [h,b], Shih-Yuan Lee [b,a]

[a] Division of Family Dentistry, Department of Stomatology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Dentistry, National Yang Ming Chiao Tung University, Taipei, Taiwan
[c] Institute of Oral Biology, National Yang Ming Chiao Tung University, Taipei, Taiwan
[d] Division of Allergy Immunology Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[e] Department of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[f] Biostatistics Task Force, Taipei Veterans General Hospital, Taiwan
[g] Division of Hospitalist Ward, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[h] Division of Endodontics and Periodontology, Department of Stomatology, Taipei Veterans General Hospital, Taipei, Taiwan

Sjögren's syndrome (SS) is a chronic autoimmune rheumatic disease characterized by a progressive lymphocytic infiltration of salivary glands, resulting in xerostomia and other oral diseases. The pathogenesis and mechanisms of SS on periodontal tissues are not well understood. Furthermore, results of two systemic reviews and meta-analyses in which compared periodontal parameters of patients with SS to healthy subjects were different. To determine whether periodontal conditions in SS were different from healthy controls, we re-examined the issue with a random-effect model, avoiding recruiting active controls and inadequate data conversion. Outcome measures included probing pocket depth (PPD), clinical attachment loss (CAL), plaque index (PI), and gingival index (GI). Recruited individuals comprised 198 patients with SS and 180 subjects for healthy controls. Quantitative analysis revealed higher PI (WMD = 0.76, 95% CI: 0.30, 1.23) and GI (WMD of total = 0.50, 95% CI: 0.01, 0.98) in SS patients who were not categorized into primary or secondary types of SS. PPD and CAL in SS patients was comparable with control subjects. However, heterogeneity was observed among included

* Corresponding author. Institute of Oral Biology, National Yang Ming Chiao Tung University No. 155, Sec. 2, Linong Street, Taipei, 11221, Taiwan.
E-mail address: cywu3@ym.edu.tw (C.-Y. Wu).

studies. Thus, results from this and previous analyses should be interpreted carefully, and a well-designed observational study regarding this issue should be conducted.

Introduction

Ranking next to rheumatoid arthritis (RA), Sjögren's syndrome (SS) is the second most common autoimmune diseases.[1] The estimated prevalence of primary SS (PSS) ranges from 0.9 to 6.0 per 1000 individual.[1] Secondary SS (SSS) occurs secondary to other autoimmune rheumatic diseases. SS is characterized by lymphocytic infiltration of salivary and lacrimal glands, leading to xerostomia and keratoconjunctivitis sicca. Moreover, one third of these patients with this disease develop systemic complications, such as renal, pulmonary or neuro-logical manifestations. Around 5% of PSS patients will develop lymphoma, the most severe complication of the disease.[1]

Periodontal conditions and dental caries are two of the most important oral health issues, regarding their prevalence. In the periodontal aspect, inflammatory and immune reactions extend deep into the periodontal tissues, causing loss of tooth-supporting connective tissues and alveolar bone, and thus, periodontal disease (PD). PD is known to be associated with adverse pregnancy outcomes, cardiovascular diseases, stroke, pulmonary diseases and diabetes.[2] A nationwide population-based study showed that patients with periodontal disease had an approximately 50% increased risk of subsequent SS.[3] On the other hand, PD is also one of the complications of diabetes, RA and systemic lupus erythematosus (SLE). Clinical attachment loss (CAL) in patients with RA is 0.6 mm deeper than in control subjects.[4] Patients with SLE had higher prevalence of bleeding on probing (BOP) and CAL, when compared to healthy subjects.[5] Thus, the hyperactive immune responses of autoimmune diseases may worsen the periodontal condition.

The tango between periodontal and systemic inflammation suggests a link-up between the progress of PD and SS. The normal capillary network in healthy gingiva is reported to be replaced by a "cobweb" structure in subjects with SS.[6] The dilated and twisting vasculization suggests the more inflammatory gingiva in SS subjects, compared to healthy individuals.[7] However, whether periodontal parameters reflect an inflamed and destructed periodontal tissue in SS subjects is still controversial. Although a previous meta-analysis conducted by de Goés Soares et al.[8] showed that plaque index (PI) and gingival index (GI) were larger in patients with SS than in controls, another one performed by Maarse et al.[9] concluded that PPD, CAL, PI and GI in SS patients are comparable to controls. The contradicting results might be caused by the neglect of converting standard errors (SE) or standard errors of means (SEM) reported in 3 studies[10–12] into standard deviation (SD) in the study of de Goés Soares et al. and including active controls in the study of Maarse et al. The potentially biased data reported in previous studies led to a demand for re-examining the issue. Thus, we re-examined differences between the periodontal status of SS and controls with the meta-analysis, avoiding using unconverted raw data and including active controls. Causes of heterogeneity were also explored by subgroup analyses and sensitivity analyses.

Materials and methods

Study selection criteria

This review was conducted according to the guide of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting in systematic reviews and meta-analyses[13] (checklist as supplement 1). Only quantitative studies that focused on the comparison of periodontal status between human subjects with or without PSS or SSS were included. To identify the link between periodontal parameters and SS, outcome indices included PPD, CAL, PI and GI. The meta-analysis of BOP was not performed because measurement tools among different studies varied.

Search methods

Published articles about human subjects were obtained from electronic databases of MEDLINE/PubMed, Web of Science, and the Cochrane database of systematic review and Embase until September 23rd, 2020. The search was conducted using the combination of the keywords (((("oral condition" OR "dental condition" OR "oral complication") OR (caries)) OR (periodontal disease)) OR (candidiasis)) AND (sjogren's syndrome). A manual search on the references of the articles in the review was also performed to identify relevant studies not identified by the search strategy created.

Quality assessment of methodological validity

Screening titles and abstracts of potentially relevant articles was performed before retrieving full articles, which were reviewed to verify if they fit all the inclusion criteria stated above. The literature selection and data extraction were done by two investigators (Y.H.C. and S.Y.W.). The quality of each study was assessed by Risk Of Bias In Non-

randomized Studies — of Interventions (ROBINS-I) tool.[14] Any disagreement on study inclusions, risk of bias assessment, or data extraction were resolved by discussions between the two investigators (Y.H.C., S.Y.W.).

Data extraction and synthesis of results

The following data items were extracted: authors, journal, publication year, countries and study institutions, diagnostic criteria, including and excluding criteria, number of subjects, study groups, ages, type and duration of SS, PPD, CAL, GI, and PI. Since distribution of PI or GI and medians of PPD were reported in the original articles of 2 studies,[15,16] data of mean and SD were retrieved from the meta-analysis performed by Maarse et al.[9] Data of SE and SEM reported in 3 studies[10–12] were converted to SD for meta-analysis before combination for meta-analysis using the statistical software RevMan version 5.4. The effect size was estimated and reported as the standard mean difference (SMD). The 95% confidence interval (CI) was also calculated. A random-effects model was used because between-study heterogeneity was expected. The pooled effect was considered significant if p was <0.05. Between-study heterogeneity was assessed using Cochrane's Q and I^2 statistics.[17] The heterogeneity was substantial if the Q test showed a significant result ($p < 0.05$) and $I^2 > 70\%$. Publication bias for each outcome of interest was also investigated, by visual assessment in the funnel plot[18] and the quantitative regression asymmetry test.[19] Heterogeneity was investigated by the subgroup analyses,[20] in which subjects were categorized into PSS, SSS and mix-SS. mix-SS, based on types of SS reported in the included studies. Mix-SS was defined as subjects whose type of SS was not defined in the included studies.

Influences of each study were analyzed with sensitivity tests.[21]

Results

Study selection and characteristics of eligible studies

The search identified 971 studies potentially relevant to the review. Based on the assessment of the titles and abstracts (Fig. 1), full texts of 9 papers[10–12,15,16,22–25] (summarized in Table 1 and Table 2) were assessed for detailed examination and were enrolled into meta-analysis. A total of 378 individuals were recruited to these studies, including 198 patients with SS and 180 subjects for the control group. The included studies published between 1991 and 2010 were conducted across an international spectrum, *i.e.*, the U.S.A, Brazil, Hungary, the UK, Denmark, Norway, and Turkey, representing participants from different cultural backgrounds.

Risk of bias

Quality assessment of the included studies is summarized in Table 3. Funnel plots (Fig. 2) and Egger's tests (Fig. 3) revealed no publication bias among the included studies. In the domain of "Bias due to confounding", several confounding factors or variations were uncontrolled among studies, so the overall risk of bias assessment of all included studies were "moderate risk of bias". The factors related to "Bias due to confounding" included SS-related factors (Table 1) and periodontal examination related factors (Table 4).
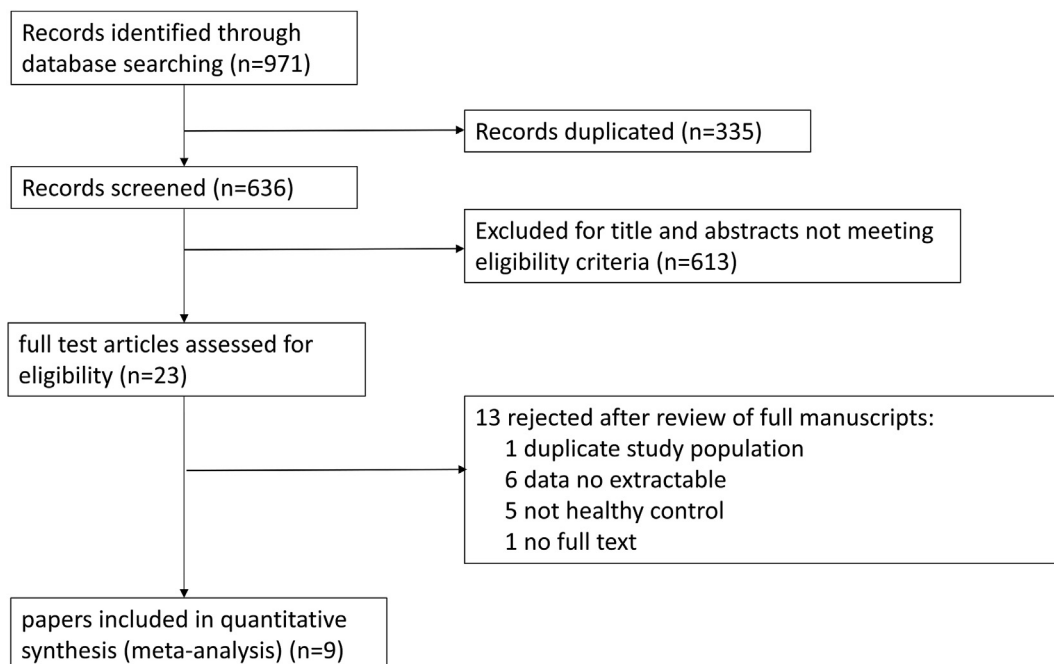

Figure 1 The PRISMA flow diagram of this study.

Table 1 Summary of the included studies.

Authors	Country	Diagnostic criteria of SS	Type of SS	Total number	N (N of females)	Age [years old] mean ± SE (range)	Duration of SS [years] mean ± SE (range)	Disease related to SSS (N)
Antoniazzi et al.[10]	Brazil	1993 European	PSS	38	11 (11)	48.1 ± 13.4 (NR)	PSS & SSS: S: 9.0 ± 5.0 (NR); D: 5.9 ± 3.7 (NR)	RA (8)
			SSS		8 (8)	53.8 ± 11.6 (NR)		
			control		19 (19)	49.8 ± 12.8 (NR)		
Ergun et al.[11]	Turkey	NR	mix-SS	52	27 (NR)	53.27 (26—78)	NR	RA (21), SLE (2)
			control		25 (NR)	54.27 (25—94)		
Kuru et al.[22]	the UK	1993 European	PSS	29	8 (8)	61.2 ± 14.4 (35—77)	D: 6.1 ± 5.7 (3—20)	
			SSS		10 (10)	60.6 ± 11.8 (43—77)	D: 8.9 ± 7.6 (3—25)	
			control		11 (11)	61.8 ± 13.9 (40—77)		
Marton et al.[23]	Hungary	2002 AECG	PSS	92	49 (46)	55 ± 11 (32—76)		
			control		43 (39)	49 ± 15 (NR)		
Najera et al.[24]	the USA	1993 European	mix-SS	49	25 (23)	60.92 ± 13.52 (28—80)	S: 7.76 ± NR (NR); D: 3.16 ± NR (NR)	RA (2)
			control		24 (22)	58.29 ± 12.09 (30—77)		
Pedersen et al.[16]	Norway	1993 European	PSS	30	16 (14)	median: 61.5 (40—80)	median: 3.5 (1—20)	
			age- and sex-matched control		14 (13)	median: 50 (39—70)		
Pedersen et al.[15]	Denmark	2002 AECG, 1986 the Copenhagen criteria	PSS	40	20 (20)	60 ± 15 (NR)	S: 10 ± 7 (NR) D: 6 ± 7 (NR)	
			age- matched control		20 (20)	56 ± 13 (NR)		
Rhodus and Michalowicz[12]	the USA	1993 European	PSS	20	10 (10)	56.7 ± NR (43—74)	D: 8.8 ± 4.8 (3—19)	
			control		10 (10)	52.6 ± NR (32—65)		
Tseng[25]	the USA	NR	mix-SS	28	14(14)	52.9 ± 11.6 (NR)	D: NR ± NR (≥5)	NR
			control		14(14)	53.7 ± 8.9 (NR)		

SS, Sjogren's syndrome; PSS, primary Sjogren's syndrome; SSS, secondary Sjogren's syndrome; mix-SS, primary Sjogren's syndrome and secondary Sjogren's syndrome; NR, not reported; SE, standard error of the mean; S: duration of symptoms; D, duration of the disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Data analysis

PPD and CAL of total SS subjects were provided in nine and five studies, respectively. The quantitative analysis revealed no deeper PPD (Fig. 4A, total) or CAL (Fig. 4B, total) in total SS patients (PPD: Weighted mean difference (WMD) = 0.20, 95% CI: −0.06, 0.45; CAL: WMD = 0.40, 95% CI: −0.08, 0.88), compared to the healthy controls. The subgroup analyses also showed that PPD or CAL in PSS, SSS or mix-SS subjects was not deeper than in controls (Fig. 4A and B: PSS, SSS and mix-SS).

PI and GI of total SS subjects were both provided in seven studies. PI (Fig. 4C, total) and GI (Fig. 4D, total) in total SS subjects were higher than in controls (PI: WMD of total = 0.53, 95% CI: 0.05, 1.01; GI: WMD of total = 0.50, 95% CI: 0.01, 0.98). However, the subgroup analyses revealed different profiles of both parameters among different groups. Quantitative analyses showed higher PI in patients with mix-SS (WMD = 0.76, 95% CI: 0.30, 1.23), but not in patients with PSS (WMD = 0.29, 95% CI: −0.37, 0.94) or SSS (WMD = 0.98, 95% CI: −0.98, 2.95; Fig. 4C). Meanwhile, GI was not higher in patients with PSS (WMD = 0.38,

Table 2 Overall parameters for primary, secondary and non-Sjögren's syndrome patients.

Studies	study groups	n	PPD (mm)	statistical association (compared to control)	statistical association (SSS compared to PSS)
Antoniazzi et al.[10]	PSS	11	2.23 ± 0.09 (SE)	$p > 0.05$	—
	SSS	8	2.62 ± 0.16 (SE)	$p < 0.05$	$p < 0.05$
	control	19	2.10 ± 0.10 (SE)	—	—
Ergun et al.[11]	mix-SS	37	1.88 ± 0.41 (SEM)	NS	—
	control	37	1.95 ± 0.63 (SEM)	—	—
Kuru et al.[22]	PSS	8	1.78 ± 0.39 (SD)	NS	—
	SSS	10	2.04 ± 0.53 (SD)	NS	NS
	control	11	2.04 ± 0.33 (SD)	—	—
Marton et al.[23]	PSS	38	2.28 ± 1.09 (SD)	$p < 0.05$	—
	control	34	1.82 ± 0.73 (SD)	—	—
Najera et al.[24]	mix-SS	25	1.92 ± 0.38 (SD)	NS	—
	control	24	1.80 ± 0.27 (SD)	—	—
Pedersen et al.[16]	PSS	16	2.32 ± 0.71 (SD)	NS	—
	control	14	2.71 ± 0.99 (SD)	—	—
Pedersen et al.[15]	PSS	20	2.36 ± 1.01 (SD)	NS	—
	control	20	2.37 ± 1.01 (SD)	—	—
Rhodus & Michalowicz[12]	PSS	10	3.49 ± 0.51 (SE)	NS	—
	control	10	3.02 ± 0.31 (SE)	—	—
Tseng[25]	mix-SS	14	3.02 ± 0.31 (SD)	NS	—
	control	14	2.82 ± 0.36 (SD)	—	—
Studies	study groups	n	CAL (mm)	statistical association (compared to control)	statistical association (SSS compared to PSS)
Antoniazzi et al.[10]	PSS	11	2.57 ± 0.20 (SE)	NS	—
	SSS	8	3.67 ± 0.50 (SE)	$p < 0.05$	$p < 0.05$
	control	19	2.40 ± 0.14 (SE)	—	—
Kuru et al.[22]	PSS	8	2.14 ± 0.65 (SD)	NS	—
	SSS	10	2.76 ± 1.79 (SD)	NS	NS
	control	11	2.60 ± 0.77 (SD)	—	—
Najera et al.[24]	mix-SS	25	2.20 ± 0.48 (SD)	$p < 0.05$	—
	control	24	1.96 ± 0.31 (SD)	—	—
Rhodus & Michalowicz[12]	PSS	10	5.44 ± 0.39 (SE)	$p < 0.10$	—
	control	10	2.70 ± 0.80 (SE)	—	—
Tseng[25]	mix-SS	14	2.70 ± 0.80 (SD)	NS	—
	control	14	2.79 ± 0.46 (SD)	—	—
Studies	study groups	n	PI	statistical association (compared to control)	statistical association (SSS compared to PSS)
Antoniazzi et al.[10]	Antoniazzi et al.14	Antoniazzi et al.14	Antoniazzi et al.14	Antoniazzi et al.14	Antoniazzi et al.14
	SSS	8	1.28 ± 0.10 (SE)	$p < 0.05$	$p < 0.05$
	control	19	0.73 ± 0.06 (SE)	—	—
Kuru et al.[22]	PSS	8	1.18 ± 0.33 (SD)	NS	—
	SSS	10	1.44 ± 0.33 (SD)	NS	NS
	control	11	1.44 ± 0.56 (SD)	—	—
Najera et al.[24]	mix-SS	25	0.96 ± 0.42 (SD)	$p < 0.05$	—
	control	24	0.65 ± 0.24 (SD)	—	—
Pedersen et al.[16]	PSS	16	0.54 ± 0.31 (SD)	NS	—
	control	14	0.52 ± 0.18 (SD)	—	—
Pedersen et al.[15]	PSS	20	0.61 ± 0.70 (SD)	NS	—
	control	20	0.60 ± 0.71 (SD)	—	—
Rhodus & Michalowicz[12]	PSS	10	0.97 ± 0.46 (SE)	$p < 0.10$	—
	control	10	0.65 ± 0.35 (SE)	—	—
Tseng[25]	mix-SS	14	0.5 ± 0.35 (SD)	NS	—

Table 2 (*continued*)

Studies	study groups	n	PI	statistical association (compared to control)	statistical association (SSS compared to PSS)
	control	14	0.32 ± 0.28 (SD)	—	—

Studies	study groups	n	GI	statistical association (compared to control)	statistical association (SSS compared to PSS)
Antoniazzi et al.[10]	PSS	11	1.15 ± 0.07 (SE)	$p < 0.05$	—
	SSS	8	1.19 ± 0.07 (SE)	$p < 0.05$	$p > 0.05$
	control	19	0.71 ± 0.05 (SE)	—	—
Kuru et al.[22]	PSS	8	1.47 ± 0.32 (SD)	NS	—
	SSS	10	1.47 ± 0.32 (SD)	NS	NS
	control	11	1.52 ± 0.65 (SD)	—	—
Najera et al.[24]	mix-SS	25	1.11 ± 0.49 (SD)	NS	—
	control	24	1.01 ± 0.33 (SD)	—	—
Pedersen et al.[16]	PSS	16	0.49 ± 0.31 (SD)	NS	—
	control	14	0.48 ± 0.30 (SD)	—	—
Pedersen et al.[15]	PSS	20	0.32 ± 0.56 (SD)	NS	—
	control	20	0.34 ± 0.60 (SD)	—	—
Rhodus & Michalowicz[12]	PSS	10	1.37 ± 0.66 (SE)	NS	—
	control	10	0.98 ± 0.36 (SE)	—	—
Tseng[25]	mix-SS	14	0.98 ± 0.36 (SD)	NS	—
	control	14	0.79 ± 0.28 (SD)	—	—

PSS, primary Sjogren's syndrome SS; SSS, secondary Sjogren's syndrome; mix-SS, primary Sjogren's syndrome and secondary Sjogren's syndrome; PPD, periodontal probing depth; CAL, clinical attachment loss; PI, plaque index; GI, gingival index; SE, standard error of the mean; SD, standard deviation; NS, not significant.

95% CI: −0.30, 1.06), SSS (WMD = 1.02, 95% CI: −1.20, 3.23) or mix-SS (WMD = 0.35, 95% CI: −0.10, 0.81) than healthy controls.

Presence of significant heterogeneity for data of PI and GI in total SS subjects is suggested (Fig. 4C and D). The subgroup analyses showed I^2 for PI of PSS, SSS and mix-SS were 71%, 89% and 0%. I^2 for GI of PSS, SSS and mix-SS were 73%, 91% and 0%, indicating the presence of the heterogeneity. Based on the visual inspection of the forest plots, the study of Antoniazzi et al.[10] was likely the outlier and contributed to the heterogeneity. The sensitivity test showed that removing the study of Antoniazzi et al.[10] led to the conclusion of no difference in PI and GI of SS patients and controls (Table 5). Additionally, opposite results of PI or GI were also obtained by removing studies of Najera et al.[24] or Tseng,[25] two studies that compared the mix-SS group with controls. Removing the study of Kuru et al.[22] also led to a conclusion that PPD and CAL were deeper in patients of SS than controls. Removing the study of Pedesen et al.[16] resulted in deeper PPD in patients of SS than controls.

Discussion

Although the comparison of periodontal parameters in SS patients with healthy controls has been reported in two meta-analyses, this study outcompeted the previous ones by (1) correctly transferring the data of SE and SEM reported in 3 studies[10−12] to SD for meta-analysis, in contrast to the study conducted by Antoniazzi et al.,[10] and (2) removing two studies[26,27] that included patients with sicca syndrome, other systemic autoimmune disease or subjects with anti-SSA/SSB autoantibodies as controls, in contrast to the study conducted by Maarse et al.[9]

This systematic review and meta-analysis showed that PI and GI in total SS patients were greater than the healthy controls. This might be due to the decrease of salivary glands functions, which are critically important for the maintenance of oral health. Xerostomia was shown to be associated with plaque accumulation and bleeding on probing.[28] The change of salivary viscosity, the decline of self-cleaning ability, the reduction of lubricating ability, the loss of antimicrobial molecules could all contribute to plaque accumulation.[10] Our study echoes with the meta-analyses conducted by de Goés Soares et al.[8] In contrast, given that "researchers should avoid categorizing active and inactive controls into a generic control group to achieve meaningful estimates",[29] estimated effects of SS in the study of Maarse et al.[9] were likely to be seriously confounded by differences in comparator group intensity.

Although the issue of heterogeneity was also detected in previous meta-analyses,[8,9] we further explored it with strategies in additions to I^2 and chi^2 tests. The subgroup analysis, which were not performed genuinely in previous

Table 3 Risk of bias evaluation of the included studies.

Domain	Antoniazzi et al.[10]	Ergun et al.[11]	Kuru et al.[22]	Marton et al.[23]	Najera et al.[24]	Pedersen et al.[16]	Pedersen et al.[15]	Rhodus & Michalowicz[12]	Tseng[25]
Bias due to confounding	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Bias in selection of participants into the study	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Bias in classification of interventions	X	X	X	X	X	X	X	X	X
Bias due to deviations from intended interventions	X	X	X	X	X	X	X	X	X
Bias due to missing data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bias in measurement of outcomes	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bias in selection of the reported result	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Overall	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk

studies, showed that PI in PSS or SSS subjects, or GI in PSS, SSS or mix-SS subjects was not severer than in healthy controls. The sensitivity test showed that inclusion of three studies,[10,24,25] two of which recruited mix-SS subjects,[24,25] led to the significantly higher PI or GI in SS subjects. These findings are threats to the validity of the results. While SS is well known for its diverse presentation of the disease, it was not surprising that characteristics of subjects were varied among different observational studies. Thus, to include studies that are *de facto* the same, the core philosophy of meta-analysis,[30] was very difficult. However, considering that the heterogeneity of PI and GI in the mix-SS subjects was absent ($I^2 = 0$, Fig. 3C and D), the higher PI and GI in the mix-SS subjects than healthy controls might be convincing.

On the other hand, the difference between the results of total SS and subgroup analyses could be explained by the insufficient sample size in each subgroup. The result could be considered as a study testing whether different periodontal parameters in SS patients were different from controls. Using data from this meta-analysis to estimate sample size, 208 subjects should be recruited for sufficient statistical power. The sample sizes for the PSS and SSS subgroups were 139 and 49, relatively. Thus, the probability of detecting an actual existing effect of PSS or SSS was relatively low. Indeed, using statistical method to increase sample size is the strength of meta-analysis.

Additionally, we were unable to exclude publication bias even though there was no funnel plot asymmetry. It is possible that negative studies were not published. The heterogeneity comes from factors that would affect periodontal parameters, which were reviewed for the first time in Table 4. The confounding factors of periodontal disease, including DM, smoking and previous periodontal history/treatment, etc., were neither controlled well in most studies. Removing the study conducted by Najera et al.,[24] which included subjects who received periodontal surgery, led to different conclusion for PI and GI (Table 5). Subjects in the included studies had different SS-diagnosed duration and medications, potentially impacting the progress of PD differently. Finally, while a study[10] reported the medication for the treatment of the SS, information about treatments of SS subjects in other studies was limited. It is unclear how treatment may modify the disease course. This systematic review included a comprehensive and systematic literature search, quantitatively and qualitatively studying most periodontal aspects in SS, including PPD, CAL, PI and GI. It also corrected biased data from previous reports.

In conclusion, outcomes of the present meta-analysis highlighted negative impacts on PI and GI in subjects with SS. However, regarding the threat from heterogeneity, reported estimates might not be solid enough to conclude the effect of SS on periodontal conditions. Thus, a well-designed research with large sample sizes, matching of co-founding factors and simultaneous observation of periodontal and glandular changes is required to identify effects of SS on periodontal tissues. Meanwhile, due to the potential impacts of low salivary flow rate on plaque accumulation, dentists should keep reinforce the teeth cleaning ability of the patients with SS.
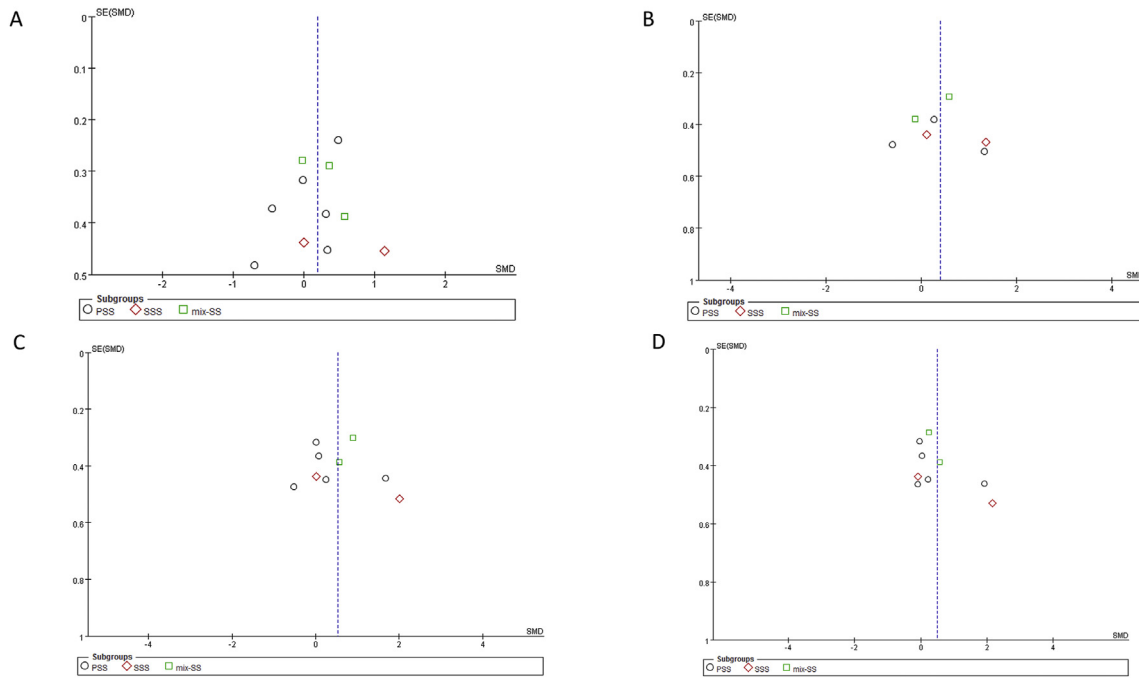
Figure 2 Funnel plots **(A)** probing pocket depth (PPD) **(B)** Clinical attachment loss (CAL) **(C)** Plaque index (PI) **(D)** gingival index (GI).
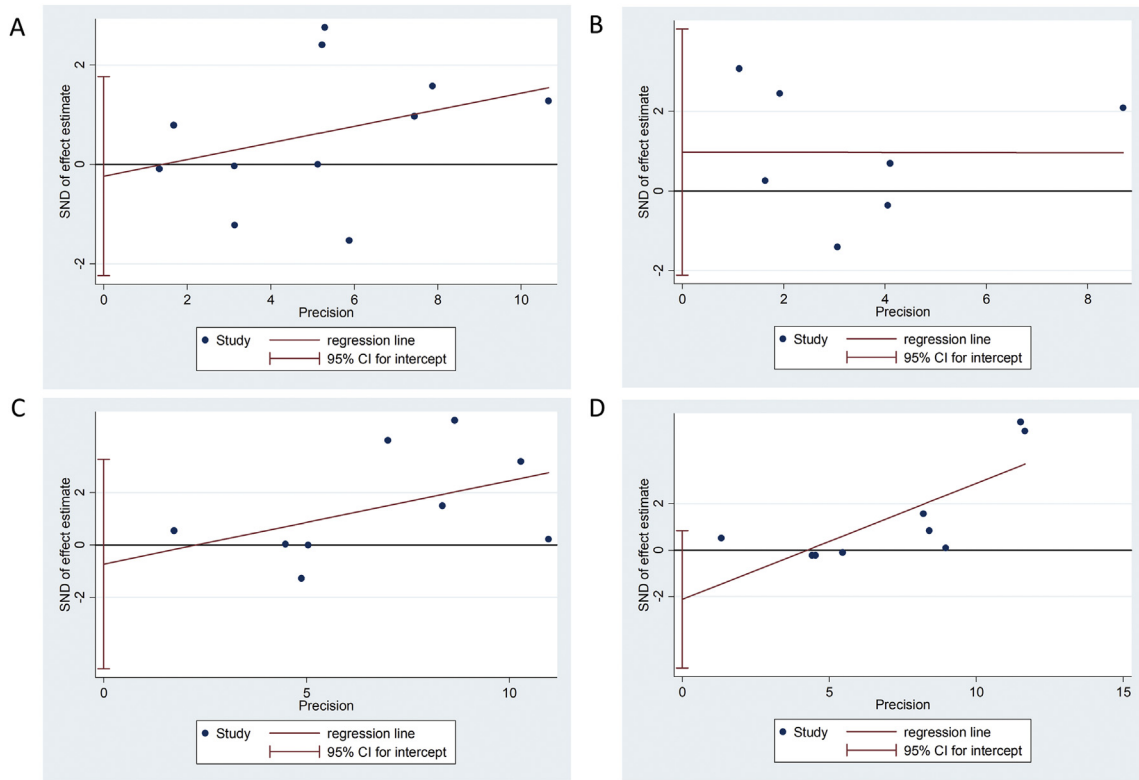

Figure 3 Egger's test **(A)** probing pocket depth (PPD) **(B)** Clinical attachment loss (CAL) **(C)** Plaque index (PI) **(D)** gingival index (GI).

Table 4 Periodontal status that is related heterogeneity.

| Author	selected teeth	probing sites/surface	Type of probes	Plaque index	Gingival index	Prior periodontal treatment	DM and smoking
Antoniazzi et al.[10]	all erupted teeth, excluding 3rd molar	PPD and CAL of six sites (mesio-buccal, disto-buccal, mesio-lingual, mid-lingual and distal lingual) of each tooth; PI and GI of four sites (mesial, buccal, distal and lingual)	indicating what kind of probe they used	Silness & Loe[31]	Loe[32]	excluding patients receiving periodontal treatment.	recruiting three, two and five heavy smokers in PSS, SSS and control groups, respectively; excluding DM patients
Ergun et al.[11]	not mentioned	four sites (buccal, mesial, lingual and distal)	Hu-Friedy periodontal probe with Williams's markings	approximal plaque index	not mentioned		
Kuru et al.[22]	all erupted teeth, excluding 3rd molar	four sites (disto-, mid-, mesio-buccal, mid-lingual)	the William's periodontal probe	Silness & Loe[31]	Loe & Silness[33]		
Marton et al.[23]	not mentioned	four sites of the selected teeth	the calibrated periodontal probe	not mentioned	not mentioned		
Najera et al.[24]	all erupted teeth, excluding 3rd molar	four sites (disto-, mid-, mesio-buccal, mid-lingual)	the Florida probe	Silness & Loe,[31] Loe[32]		five SS subjects and three control subjects who had received periodontal surgery	excluding DM patients in the control group
Pedersen et al.[16]	Ramfjord teeth	four sites (buccal, mesial, lingual and distal)	manual periodontal probe proposed by Loe	Loe[32]	Loe[32]		recruiting three smokers but no smokers in the control group
Pedersen et al.[15]	Ramfjord teeth	four sites (buccal, mesial, lingual and distal)	manual periodontal probe proposed by Loe	Loe[32]	Loe[32]		recruiting five smokers but no smoker in the control group
Rhodus and Michalowicz[12]	Ramfjord teeth	six sites of the selected teeth.	Michigan "O" probe with Willian's marking	not mentioned		excluding patients receiving periodontal treatment	excluding smokers
Tseng[25]	Ramfjord teeth +26	mesio-facial surfaces of upper right first molar, upper left first premolar and first molar and lower right central incisor, and mesio-lingual surfaces of upper left central incisor, left lower first molar and lower right first premolar	Michigan "O"probe with Willian's marking	Loe[32]	Silness & Loe[31]		
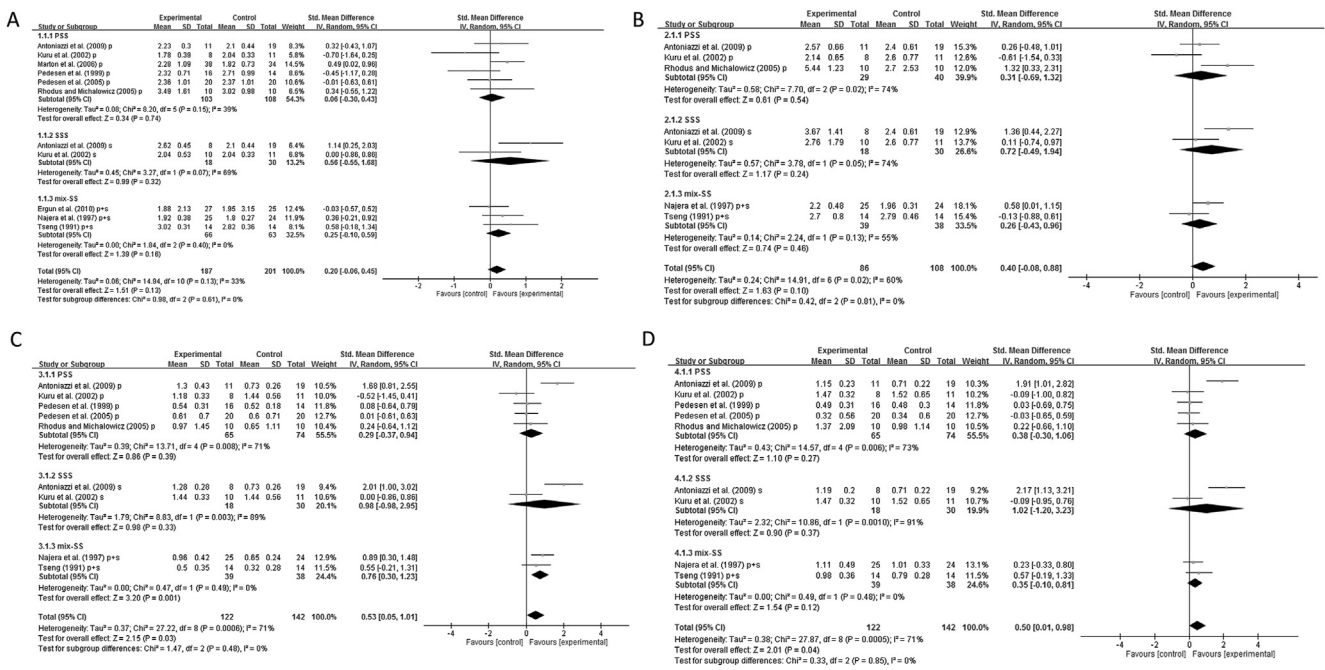
Figure 4 Forest plots showing the weighted mean difference (WMD) between Sjögren's Syndrome (SS) patients and non-SS patients **(A)** probing pocket depth (PPD) **(B)** Clinical attachment loss (CAL) **(C)** Plaque index (PI) **(D)** gingival index (GI).

Table 5 Sensitivity analyses of included studies.

Indices	Excluded study	Standard mean difference (95% CI)	Heterogeneity (I^2), %
PPD	Antoniazzi et al.[10]	0.12 (−0.13, 0.38)	22
	Kuru et al.[22]	0.27 (0.02, 0.53)*	26
	Marton et al.[23]	0.15 (−0.13, 0.43)	32
	Pedesen et al.[16]	0.26 (0.01, 0.51)*	22
	Pedesen et al.[15]	0.22 (−0.06, 0.50)	38
	Rhodus and Michalowicz[4]	0.19 (−0.09, 0.46)	39
	Ergun et al.[11]	0.23 (−0.06, 0.51)	36
	Najera et al.[24]	0.18 (−0.11, 0.46)	39
	Tseng[25]	0.16 (−0.11, 0.43)	36
CAL	Antoniazzi et al.[10]	0.25 (−0.32, 0.82)	60
	Kuru et al.[22]	0.62 (0.09, 1.14)*	56
	Rhodus and Michalowicz[4]	0.27 (−0.20, 0.75)	55
	Najera et al.[24]	0.36 (−0.23, 0.95)	65
	Tseng[25]	0.49 (−0.04, 1.02)	60
PI	Antoniazzi et al.[10]	0.23 (−0.11, 0.58)*	32
	Kuru et al.[22]	0.73 (0.20, 1.25)	70
	Pedesen et al.[16]	0.59 (0.05, 1.12)	73
	Pedesen et al.[15]	0.60 (0.07, 1.14)	71
	Rhodus and Michalowicz[4]	0.56 (0.03, 1.10)	74
	Najera et al.[24]	0.48(−0.07, 1.02)*	72
	Tseng[25]	0.53 (−0.02, 1.07)*	74
GI	Antoniazzi et al.[10]	0.13 (−0.14, 0.41)*	0
	Kuru et al.[22]	0.66 (0.08, 1.25)	76
	Pedesen et al.[16]	0.56 (0.02, 1.11)	74
	Pedesen et al.[15]	0.58 (0.03, 1.12)	73
	Rhodus and Michalowicz[4]	0.53 (−0.1, 1.08)*	75
	Najera et al.[24]	0.55 (−0.03, 1.12)*	75
	Tseng[25]	0.49 (−0.06, 1.04)*	75

PPD, periodontal probing depth; CAL, clinical attachment loss; PI, plaque index; GI, gingival index; SE, standard error of the mean; SD, standard deviation; CI: confident interval.
* indicating results that are different from the data present in the meta-analysis of Fig. 4.

Declaration of competing interest

Acknowledgement

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