Sjögren's syndrome is not a risk factor for periodontal disease: a systematic review

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ABSTRACT

Objective. *Sjögren's syndrome (SS) is an autoimmune disorder causing irreversible damage to the exocrine glands. Evidence whether SS patients are at a higher risk to develop periodontal disease is conflicting. Therefore, we systematically reviewed the literature on the prevalence of periodontal disease in patients with SS.*

Methods. *Searches were performed in MEDLINE and CENTRAL databases on prevalence of periodontal diseases in SS. Meta-analyses were performed for gingival index (GI), plaque index (PI), probing pocket depth (PPD), clinical attachment level (CAL), DMFT and DMFS (Decayed Missing Filled Teeth, respectively, Surfaces).*

Results. *Out of 512 studies, 10 studies were eligible for quantitative synthesis. Meta-analyses of the data indicated that in SS patients CAL, GI, PPD and PI are comparable to controls. DMFT and DMFS values were higher in SS patients than controls.*

Conclusion. *No significant differences in the GI, PI, CAL, and PPD were observed in patients with SS compared to controls. These results indicate that there is no evidence of a higher risk for periodontal disease in patients with SS, while SS patients are more susceptible to caries compared to non-SS patients.*

Introduction

Sjögren's syndrome (SS) is an autoimmune disorder causing chronic inflammation and irreversible damage of the exocrine glands. SS is characterised by mononuclear infiltrates and IgG-producing plasma cells in the salivary and lacrimal glands. This infiltration leads to irreversible destruction of glandular tissue with a subsequent decrease in saliva secretion rate (1-3). Because of this hyposalivation, patients with SS suffer from a sensation of oral dryness (xerostomia) and its related complaints (eating and swallowing problems, lack of taste, speech problems), and are prone to developing progressive dental decay and inflammation of the oral mucosa (4). Increased incidences of dental caries in patients with SS have been reported, which ultimately may lead to loss of teeth (2, 5-7).

In addition to dental caries, periodontal disease can also result in tooth loss (8). Periodontitis is a chronic bacterial infection that stimulates a host inflammatory response, leading to periodontal tissue damage that involves progressive loss of the tooth-supporting tissues such as periodontal ligament and bone. The aetiology of periodontal disease is a combination of bacterial, genetic, and lifestyle factors and the presence of other systemic diseases such as diabetes (8). Periodontal disease has also been linked to rheumatoid arthritis as periodontal disease and rheumatoid arthritis share etiological factors (9).

An imbalance between commensal microorganisms, the hosts' defense and oral hygiene could result in accumulation of bacteria on the tooth and gingival surface, causing inflammation of the gingiva. The early stage of inflammation, known as gingivitis, is characterised by an inflamed aspect of the gingiva (swelling and redness) and bleeding on probing. More advanced periodontal inflammation is known as periodontitis, which is clinically characterised by enhanced pocket-probing depths, attachment loss, and vertical and angular bone defects (10).

Previous research has been unable to show conclusive scientific evidence regarding whether patients with SS are more prone to display signs of peri-

odontal disease than non-SS patients. Some studies have suggested that SS patients may be at a higher risk of developing periodontal problems because of more gingival inflammation (11-13). In a recent review and meta-analysis, de Goés Soares (14) did not provide strong evidence that periodontal status is affected by SS. Unfortunately, that study did not include a comprehensive meta-analysis of all the available data. Therefore, we performed a systematic review of the literature in which we requested missing information from the corresponding authors to properly use all the knowledge available from the research performed in clinical settings until 2017.

The objective of our study was to assess, through a systematic review of the literature and thorough analysis of the underlying data, the risk of periodontal disease in SS *versus* non-SS patients.

Materials and methods

This study was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (15). The protocol for this systematic review was registered on PROSPERO (ID CRD42018102366) and is available on https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=102366.

Type of studies

For this research, cohort studies, case series, case-control studies, cross-sectional studies and clinical trials were considered for evaluation. Case series with <10 patients were not considered for inclusion. Reviews and animal studies were excluded. Language was restricted to English and Dutch.

Type of participants

The selected studies included a group of adult patients with SS and a non-SS control group.

Types of outcome measures

The plaque index (PI, *i.e.* a measurement of the state of oral hygiene based on recording both soft debris and mineralised deposits on teeth number 16, 12, 24, 36, 32, and 44, gingival index (GI, *i.e.* measure for the assessment of the gingival condition and records qualitative changes in the gingiva. GI scores the marginal and interproximal tissues separately on the basis of 0 to 3. The criteria are:

0 = normal gingiva; 1 = mild inflammation – slight change in colour and slight oedema, but no bleeding on probing; 2 = moderate inflammation – redness, oedema and glazing, bleeding on probing; 3= severe inflammation – marked redness and oedema, ulceration with tendency to spontaneous bleeding. The bleeding is assessed by probing gently along the wall of soft tissue of the gingival sulcus. The GI of an individual can be obtained by adding the values of each tooth and dividing by the number of teeth examined), pocket-probing depth (PPD, *i.e.* measurement of the depth of a sulcus or periodontal pocket determined by measuring distance from the gingival margin to the base of the sulcus or pocket using a periodontal probe), and clinical attachment loss (CAL, *i.e.* a measurement of the position of the gingival margin in relation to the cemento-enamel junction (CEJ) that is a fixed point that does not change throughout life. Two measurements are used to calculate the CAL: the probing depth and the distance from the gingival margin to the CEJ measured using a periodontal probe. These measurements combined result in the CAL and is directly linked to periodontal disease. In addition, DMFT (Decayed Missing Filled Teeth) and DMFS (Decayed Missing Filled Surfaces) were assessed. DMFT and DMFS give additional information on the general state of the dentition in patients. DMFT and DMFS are means to numerically express the caries prevalence and are obtained by calculating the number of Decayed (D), Missing (M) Filled (F) Teeth (T) or Surfaces (S). It is an estimation to what extend the dentition until the day of examination has become affected by dental caries.

Search strategy, screening, and selection

A literature search was conducted through the MEDLINE-PubMed, CENTRAL, EMBASE, Science Direct database, and Google Scholar. A search with the term Sjögren's syndrome in combination with the terms periodontitis, periodontal disease, gingival index, plaque index, probing depth, and clinical attachment loss was conducted for studies in English up to July 2017: ("Sjögren's syndrome"[MeSH Terms] OR ("Sjögren's"[All Fields] AND "syndrome"[All Fields]) OR "Sjögren's syndrome"[All Fields]) AND periodontal[All Fields]) OR ("periodontal index"[MeSH Terms] OR ("periodontal"[All Fields] AND "index"[All Fields]) OR "periodontal index"[All Fields] OR ("gingival"[All Fields] AND "index"[All Fields]) OR "gingival index"[All Fields])) OR ("dental plaque index"[MeSH Terms] OR ("dental"[All Fields] AND "plaque"[All Fields] AND "index"[All Fields]) OR "dental plaque index"[All Fields] OR ("plaque"[All Fields] AND "index"[All Fields]) OR "plaque index"[All Fields])) OR (probing[All Fields] AND pocket[All Fields] AND depth[All Fields])) OR (clinical[All Fields] AND attachment[All Fields] AND loss[All Fields]).

Subsequently, references of included studies were also searched for additional relevant publications. Titles, as well as the abstracts were screened by two independent reviewers [SA and FM]. If eligible aspects were present in the title or abstract, full-text articles were obtained when possible. Both examiners performed analysis of the text for the additional selection. Papers that fulfilled all inclusion and selection criteria were further processed for data extraction. In case of disagreement between the two reviewers, a third observer (HB) made the decision regarding inclusion/exclusion.

Assessment of heterogeneity

The heterogeneity amongst studies was determined with regard to the study design, subject characteristics, screening method and clinical indices.

Quality assessment

Evaluation of the methodological quality was performed with the Newcastle-Ottawa Quality Assessment Scale for case-control studies as recommended

by the Cochrane Handbook for Systematic Reviews of Interventions (16). A quality assessment tool based on this scale was used to determine the value of the case-control studies. Criteria were designed for domain selection, comparability and exposure. Selection was assessed by the case definition being adequate and independently validated. The representativeness of the cases was considered alongside the selection and definition of the control group (*e.g.* presence of potential selection biases or consecutive representative series of cases). Comparability of cases and controls on the basis of the design or analysis were included. Ascertainment of exposure, usage of the same method of ascertainment for cases and controls, as well as the degree of non-response rate were evaluated (17, 16).

Both observers generated a score for the included articles, expressed in points based on the above-mentioned criteria. In case of disagreement, a third observer (HB) made the decision regarding the score.

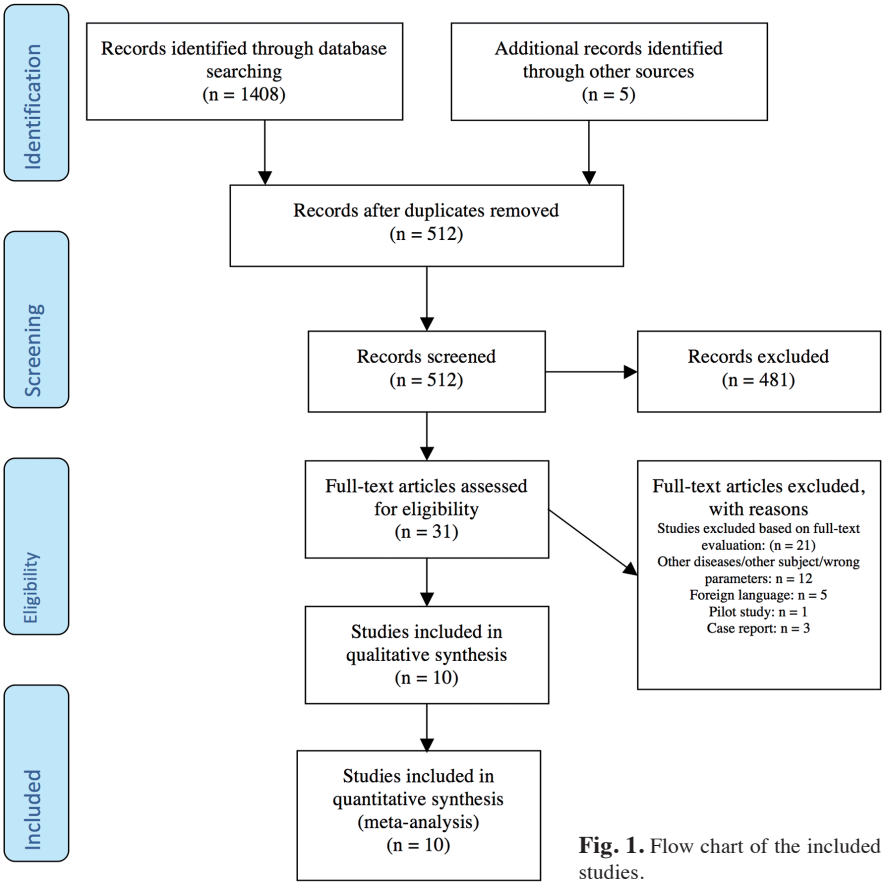


Fig. 1. Flow chart of the included studies.

Data extraction

Two review authors (SA and FM) extracted data independently with help of data extraction forms and outcome data was summarised into Review Manager (RevMan 5.3). Details of the study such as the authors, year of publication, number of patients with SS, number of controls, disease duration; smoking habits, GI, PI, CAL, average PPD, and DMFT and/or DMFS were extracted for each study and documented in a data sheet. In case of missing or incomplete data, the corresponding author was contacted to provide this information. In four cases, additional data were provided by the authors (7, 18-20); in one case, the author reported that the data were no longer available (21); and in two cases, the authors were unresponsive (12, 22).

Statistical analysis

All included studies reported one or more of the following parameters: PI, GI, PPD, CAL, DMFT, or DMFS. A meta-analysis was performed, and the differences in the means were calculated using the statistical software package Review Manager 5.3 with a "fixed effects" model for CAL, DMFT, and DMFS and a "random" model for PI, GI, and PPD. Data were summarised and presented in a descriptive manner.

Results

Search and selection results

The search resulted in a total of 1408 publications. Subsequently, five additional publications were retrieved from the reference lists of the included studies. After scanning the titles and abstracts and eliminating duplicated articles, 512 studies were selected for abstract evaluation. After further selection, 31 full-text studies were assessed and screened for eligibility. Twenty-one articles were excluded based on the eligibility criteria. One study initially did not meet the quality criteria for this review but after additional data from the authors the study could be included (20). Finally, ten articles fulfilled the inclusion criteria and were assessed methodologically for heterogeneity, data extraction, quality, and additional analyses (Fig. 1, Tables I and II) (7, 11, 13, 18, 20, 22-26).

Assessment of heterogeneity

Considerable heterogeneity was observed in all studies regarding the study design, subject characteristics, method of screening, and the clinical indices. Information regarding the type of study, location where the study was conducted, study population, and the criteria used are presented in Tables I and II.

Study design and subject characteristics

All ten studies used a cross-sectional design. In all studies, a group of SS patients enrolled in the research clinic was included. In total 228 patients were included in the SS group and 223 in the control group. The controls were subjects without SS selected at the same clinics and matched with regard to age and sex (Table I). In one study the control group was comprised of patients with subjective sicca complaints but without Sjögren's syndrome (22) and in one study the control group was comprised of oral lichen planus patients without hyposalivation or sicca complaints (20). From the SS patients, 140 were primary

Table I. Characteristics of the included studies.

Authors (year)	Study design	Location	no. of subjects	Mean age (years)	Groups	SS classification criteria	Authors' conclusion
Antoniazzi *et al*. (2009)	Cross-sectional	Private Clinic and Department of Rheumatology, Independência Hospital, Porto Alegre, Brazil.	pSS 11 sSS 8 CG 19	pSS 48.1 sSS 53.8 CG 49.8	Subjects: s: one primary SS group, one secondary SS group Controls: healthy	European classification criteria for SS	*SS seemed to negatively affect the periodontal condition, because gingival inflammation was more evident in the individuals with SS, particularly those with secondary SS.*
Ergun *et al*. (2010)	Cross-sectional	Department of Rheumatology, Istanbul University, Istanbul, Turkey.	pSS 11 sSS 16 CG 25	SS 53.27 CG 54.27	Subjects: mixed pSS and sSS Controls: healthy	NS	*SS patients may carry a higher risk of having periodontitis; however, they do suffer significantly more often from oral manifestations such as angular cheilitis and candida infestations than non-SS patients.*
Kuru *et al*. (2002)	Cross-sectional	Department of oral Medicine Eastman Dental Institute, University College London, UK.	pSS 8 sSS 10 CG 11	pSS 61.2 sSS 60.6 CG 61.8	Subjects: one pSS group, one sSS group Controls: healthy	European classification criteria for SS	*No significant differences in the sub-gingival plaque samples from control, primary, or secondary SS patients for the peptidase activity test, frequency, or type of periodontal micro-organisms were observed.*
Le Gall *et al*. (2016)	Cross-sectional	Department of Rheumatology, CHRU de Brest, France.	pSS 31 CG 42	pSS 60.0 CG 55.1	Subjects: pSS Controls: subjectivesicca complaints	AECG	*Results suggests that patients with SS have more severe periodontal conditions than non-SS patients.*
Márton *et al*. (2006)	Cross-sectional	3rd Department of Internal Medicine, University of Debrecen, Hungary.	pSS 38 CG 34	pSS 55 CG 49	Subjects: pSS Controls: healthy	AECG	*No differences were observed in the severity of periodontal disease between patients and controls.*
Najera *et al*. (1997	Cross-sectional	Salivary Dysfunction Clinic, Baylor College of Dentistry, Dallas, TX, USA.	pSS 23 sSS 2 CG 24	pSS + sSS 60.92 CG 58.29	Subjects: mixed pSS and sSS Controls: healthy	European classification criteria for SS	*Although no significant difference was found in the number of cases of "established periodontitis" between the SS and controls, odd ratio analysis suggests that patients with SS have a 2.2-times higher risk of having adult periodontitis than healthy controls.*
Pedersen *et al*. (1999)	Cross-sectional	School of Dentistry, University of Copenhagen, and the Dental Department, Rigshospitalet, Copenhagen, Denmark	pSS16 CG 14	pSS 61.4 CG 50	Subjects: pSS Controls: healthy	European classification criteria for SS	*PI, GI, and PPD did not differ significantly.*
Pedersen *et al*. (2002)	Cross-sectional	Copenhagen Gerodontological Oral Health Research Center, School of Dentistry, University of Copenhagen, Denmark.	pSS: 20 CG: 20	pSS: 64.1 CG: 64.8	Subjects: pSS Controls: Oral lichen planus patients	European classification criteria for SS and the Cophenhagen criteria	*The pSS patients had more systemic diseases, medication intake, oral dryness, poorer general health and lower salivary secretion than the OLP patients, who had the highest plaque index (PI).*
Pedersen *et al*. (2005)	Cross-sectional	School of Dentistry, University of Copenhagen, Denmark.	pSS 20 CG 20	pSS 60 CG 56	Subjects: pSS Controls: healthy	European classification criteria for SS and the Cophenhagen criteria	*The SS patients were characterised by having lower salivary flow rates, better oral hygiene habits, slightly higher gingival scores, but similar plaque scores compared to other groups. Regarding the other periodontal measures, the presence of periodontal disease is not substantially increased in pSS.*
Tseng (1991)	Cross-sectional	Department of Oral Diagnosis, School of Dentistry, University of Minnesota, Minneapolis, MN, USA.	SS 14 CG 14	SS 52.9 CG 53.7	Subjects: SS (not defined) Controls: healthy	NS	*No significant differences were found for GI, PI, BI, PPD, and CAL.*

SS: Sjögren's syndrome; pSS: primary Sjögren's syndrome; sSS: secondary Sjögren's Syndrome; CG: control group; AECG: American European Consensus Group; NS: not specified.

Sjögren's syndrome (pSS) patients and 46 were secondary Sjögren's syndrome (sSS) patients. Two studies (52 patients) were unclear about whether the patients were primary or secondary SS patients (25, 26). The mean disease duration (*i.e.* time from established diagnosis to examination) was provided in seven of the ten included studies and was 3.0 years (7, 11, 18, 22-25).

Smoking habits were reported in seven of the ten included studies (7, 11, 18, 20, 22, 23, 25). Overall, in the SS group 24 patients and in the control group 13 patients were smoking.

Table II. Risk of bias analysis of the included studies.

	Is the case definition adequate? (1)	Selection and representativeness of the cases (2)	Selection of controls (3)	Definition of controls (4)	Comparability of cases and controls on the basis of the design or analysis (study adjusted for age, sex) (5)	Outcome same method of ascertainment for cases and controls (6)	Non-response rate (7)	Score
Antoniazzi *et al. 2009*	*	*	-	*	**	*	*	7/8
Ergun *et al.* 2010	*	*	*	*	*	*	*	7/8
Kuru *et al. 2002*	*	*	-	*	**	*	*	7/8
Le Gall *et al. 2016*	*	*	-	-	*	*	*	5/8
Márton *et al. 2006*	*	*	*	-	**	*	*	7/8
Najera *et al. 1997*	*	*	*	*	**	*	*	8/8
Pedersen*et al. 1999*	*	*	-	*	**	*	*	7/8
Pedersen *et al. 2002*	*	*	-	*	*	*	*	6/8
Pedersen *et al. 2005*	*	*	-	*	**	*	*	8/8
Tseng 1991	*	*	*	*	*	*	*	8/8

Criteria 1, 2, 3, 4, 6, 7: not clear or not adequate; * adequate. Criteria 5: not clear or not adequate; *partially adequate; ** adequate.

Different criteria were used to establish the diagnosis 'Sjögren's Syndrome'. In five studies (11, 18, 20, 23, 24) the European Classification criteria for Sjögren's syndrome were used (7), in three studies (7, 22, 25) the American-European Consensus Group (AECG) criteria were used (27), and in two studies this was not clearly reported (13, 26).

In each study, a single examiner performed periodontal and oral examination of all subjects. Blinding of this investigator with regard to subjects (SS or controls) was unclear in all studies. Subjects who were already under periodontal treatment were excluded in all studies.

Clinical parameters and meta-analyses

Eight studies reported the GI, and four them reported a significant difference between the SS and control group, while the other four reported no difference. A meta-analysis comprising 163 SS patients and 164 controls showed no significant difference in the GI (mean difference: 0.13; 95%CI: -0.10 – 0.20; p=0.20; Fig. 2 panel A). PI was reported by eight studies, of which five showed a significant difference. The meta-analysis including 163 SS patients and 164 controls did not show a significant difference in PI (mean difference: 0.17; 95%CI:-0.08–0.42; p=0.17; Fig. 2 panel B). Four of the ten studies reported CAL, of which two reported a significant difference. A meta-analysis comprising 76 SS patients and 68 controls showed no significant difference with respect to CAL (mean difference: 0.10; 95%CI:-0.29–0.49; p=0.60) (Fig. 2 panel C). All ten studies reported data for PPD, only two reported a statistically significant difference. Also, no significant difference was found for PPD in the meta-analysis (228 SS patients, 223 controls; mean difference: 0.12; 95%CI:-0.04–0.28; p=0.14) (Fig. 2 panel D). Three studies reported a DMFT index and two reported a DMFS index. All of them reported a significant difference between SS and control patients. This corresponds with the meta-analysis that found a significant difference for DMFT (mean difference: 4.42; 95%CI:2.44–6.41, p=0.0001) (Fig. 2 panel E). Unfortunately, DMFS was reported only 2 studies therefore a meta-analyses was not possible.

Primary versus secondary Sjögren's syndrome

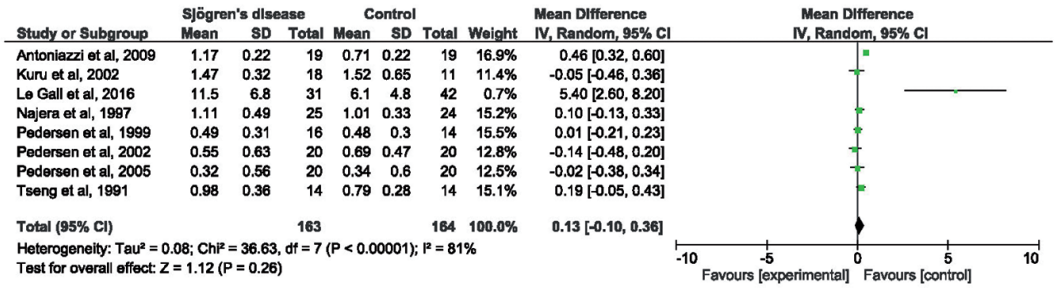
Most studies did not distinguish between pSS and sSS. Three studies included only pSS patients (7, 18, 20) and two studies compared both groups (23, 24). One of the latter studies reported significantly higher pocket depths and clinical attachment loss in sSS patients compared to pSS patients (23), while the other study found non-significant increases of these parameters in sSS patients (24) (Table III).

Discussion

This systemic review assessed whether patients with SS are more prone to develop symptoms of periodontal disease. Several studies concluded that there was no increased risk of periodontal disease in patients with SS compared to controls (7, 18, 20, 24-26), whereas in other studies reported that the risk on developing periodontal disease was increased in SS patients (11, 13, 22, 23). The meta-analyses conducted in our study showed that all the outcome measures were higher in the SS group compared to the non-SS group but these differences were not significant except for DMFT.

Salivary secretion in SS patients as well as the related self-clearance of the oral cavity is reduced in SS patients. As a result, debris will more easily collect and remain on the tooth surfaces in SS subjects than in non-SS controls. This is reflected by the slightly higher gingival health indices and pocket-probing depth values in the SS patients than in their matched controls. As a result, in SS patients, the marginal tissue could be more prone to continuous inflammatory insults. This will probably have resulted in slightly more gingival swelling, bleeding and increased pocket-

A



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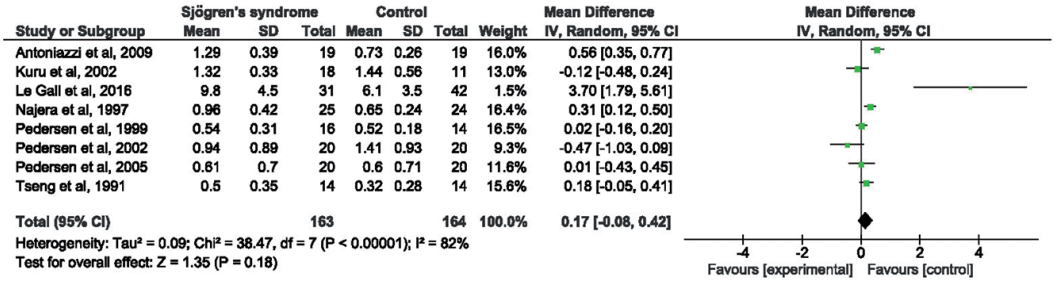

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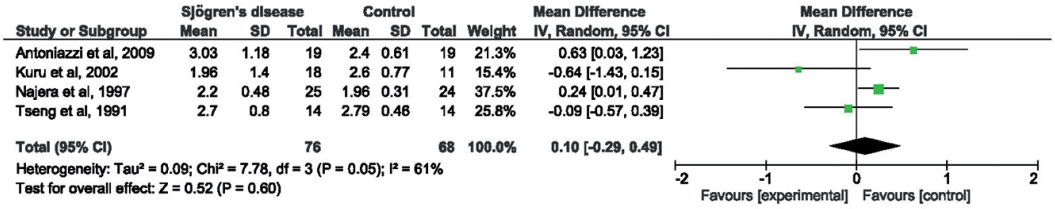

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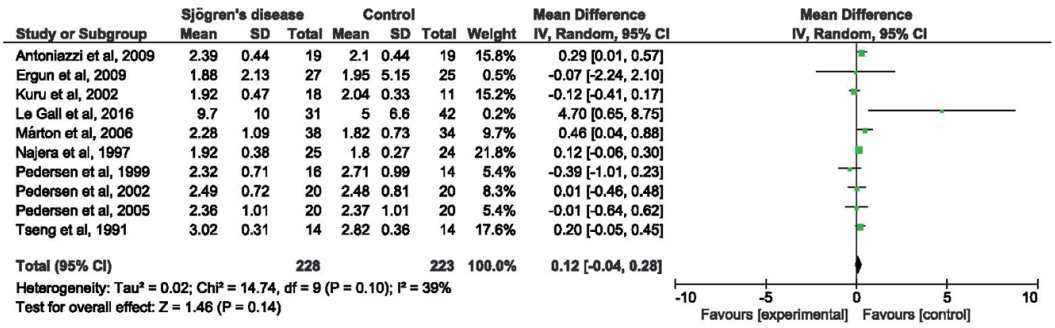

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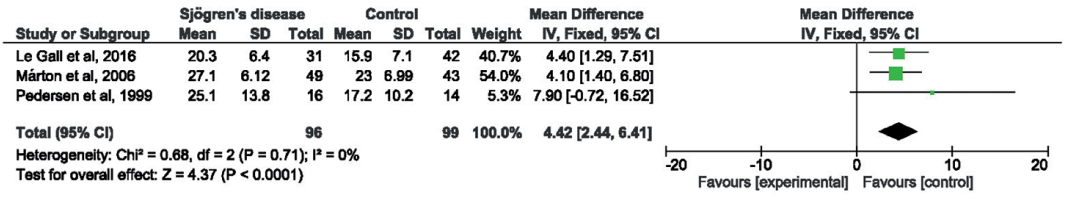

Fig. 2. Forest plots of
A: gingival index
B: plaque index
C: clinical attachment loss
D: probing pocket depth
E: DMFT

Table III. Gingival index (GI), plaque index (PI), probing pocket depth (PPD) and clinical attachment loss (CAL) of studies presenting data on patients with primary and/or secondary Sjögren's syndrome.

Parameter	Study	pSS			sSS			*p*-value
		Mean	SD	n	Mean	SD	n	
GI	Antoniazzi	1.15	0.23	11	1.19	0.20	8	0.754
	Kuru	1.47	0.32	8	1.47	0.32	10	1.000
	Pedersen 1999	0.49	0.31	16				
	Pedersen 2005	0.32	0.56	20				
	Pedersen 2002	0.55	0.63	20				
PI	Antoniazzi	1.30	0.43	11	1.28	0.28	8	0.910
	Kuru	1.18`	0.33	8	1.44	0.33	10	0.116
	Pedersen 1999	0.54	0.31	16				
	Pedersen 2005	0.61	0.7	20				
	Pedersen 2002	0.94	0.89	20				
PPD	Antoniazzi	2.23	030	11	2.62	0.45	8	0.036
	Kuru	1.78	0.39	8	2.04	0.53	10	0.264
	Pedersen 1999	2.32	0.71	16				
	Pedersen 2005	2.36	1.01	20				
	Pedersen 2002	2.49	0.72	20				
CAL	Antoniazzi	2.57	0.66	11	3.67	1.41	8	0.036
	Kuru	2.14	0.65	8	2.76	1.79	10	0.0357

probing depths in SS patients, although not clinically relevant and none of the measured parameters was significantly higher.

Three of the ten included studies also investigated the difference in DMFT score and evidence was found that SS patients are more susceptible to caries than non-SS patients. A change in DMFT describes the dental caries experience from childhood until the day of examination and gives an indication of future dental health. As we have shown in a previous study the high incidence of caries in SS patients results in a higher loss of teeth compared to a non-SS control group (29). The rapid caries process resulting in an early loss of teeth could be an additional explanation for the comparable risk for developing periodontal disease between both groups. Patients in the SS-group lose their teeth due to a rapid onset of caries before they can develop periodontal disease. This is also found in patients with hyposalivation due to radiotherapy (30). Furthermore, in a study using an in vivo model in which onset, progression, and prevention of hyposalivation-related dental caries could be studied, it was found that severe demineralisation of enamel occurred within 6 weeks in hyposalivation patients (31).

Often dental implants are used to replace missing teeth in these patients. Fortunately, a previous study showed comparable results for dental implants with regard to periodontal health, as we have found for natural teeth in the current study (32). In that study it was found that SS patients seemed to have more signs of peri-implant soft tissue infection but comparable pocket-probing depths compared to healthy controls. Therefore, dental implants are a viable treatment option for replacing teeth lost due to caries in SS patients.

All of the included studies used a combination of several periodontal parameters. For the best possible evaluation of periodontal health, bone and attachment loss around teeth should be assessed by combining measurement of bone loss on standardised intraoral dental radiographs together with the periodontal parameters used in the included studies (33, 34). Unfortunately, none of the included studies used a combination of periodontal parameters and radiographic analysis, which limits our conclusions. Also, the inflammatory burden of existing disease was not scored, which can now be done with the Periodontal Inflamed Surface Area score (PISA) (35).

Smoking habits were reported in seven of the ten included studies (7, 11, 18, 20, 22, 23, 25) whereas the other studies did not specify whether the SS or control group comprised patients with current tobacco use. Overall, 24 SS patients and 13 controls were smoking. It is known that frequent use of tobacco is associated with a higher risk of periodontal disease (34, 36). However, the impact of smoking on our meta-analyses is considered limited, given the fact that the numbers of subjects that use tobacco were low and comparable in the studies included in the present review.

Another known risk factor for periodontal disease is rheumatoid arthritis (RA) (37). An autoimmune disease, such as RA, accompanies the secondary form of SS. Although the literature in this regard is inconsistent, about 4–31% of the SS patients also have RA (38). Studies report that periodontal disease is approximately twice as common and more severe in patients with RA. In addition, it is suggested that there is a dose-response pattern in the association between the severity of periodontitis and RA disease activity (9, 39). A recent study reported significantly higher PPD, CAL and PI in RA patients compared to non-RA patients. These results suggest that RA patients have a higher risk of developing periodontal disease compared to non-RA (40, 41). It is estimated that 4-31% of SS patients also have RA (3) and, as there seems to be a link between periodontal disease and rheumatoid arthritis, sSS patients with RA as associated disease could have an additional risk in developing periodontal disease. To eliminate the potential overestimating effect of RA on periodontal parameters in our study, either all patients with RA should be excluded or only patients with pSS should be included. Unfortunately, only two studies presented data on pSS and sSS patients separately (23, 24), and three studies included only pSS patients (7, 18, 20). Of the two studies comparing pSS and sSS, one study reported significantly higher pocket depths and clinical attachment loss in sSS patients (23), while the other study found non-significant increases of these parameters in sSS patients (24). For GI and PI, no significant differences between pSS and sSS were found. Although significant differences were found for pocket probing depths and clinical attachement loss between RA patients and controls, these

differences are of a low magnitude and clinically probably not relevant. Further studies exploring the potential contribution of RA to the risk of developing periodontal disease in sSS patients are warranted.

In two studies it was unclear which classification criteria were used to diagnose SS (13, 26). According to Manthorpe *et al*., focusing on the symptomatology and the subjective symptoms can lead to misclassification. Thus, objective test results should be the most important criteria in diagnosing SS (42). In the other studies included in our meta-analysis, however, the sample of patients with SS has been carefully characterised and selected according the European Classification for SS or, the AECG criteria, while the are not yet eligible studies applying the 2016 ACR-EULAR criteria for classifying SS and assessing periodontal disease (43). The European classification for SS is a precursor of the AECG criteria. There are some differences between these two but these are considered small and are mainly based on modifications that make the classification criteria more precise and the tests more broadly applicable (27).

For qualitative analysis, the Newcastle-Ottawa Quality Assessment Scale for case-control studies was used. In the current literature, the opinions on this scale differ. Proponents found the tool easy to use, valid, and reliable (17). Opponents, however, point out that blinding of the investigator contributes disproportionally to the final score (44, 45). For the included case-control studies, none of the studies described whether the investigator performing the oral examination was unaware whether the subject was SS patient or healthy control, which leads to an uncertain ascertainment of exposure. The estimated risk of bias is therefore likely to increase. A higher score was given to population-based controls compared with hospital controls or controls from the same clinic (44, 45). Although there is still a lack of agreement about this topic, cautiousness is advised when preferring community controls to hospital controls. To what extent this might affect the present study is questionable, as one of the ten studies did not fulfill this criterion (23). The other locations were either hospitals or dental schools, which make it arguable that these controls should be considered true hospital controls.

As mentioned before, subjects who underwent periodontal treatment were excluded in all studies. This could have affected the severity of periodontal disease in the experimental groups, especially since in the studies used for this meta-analysis it was not clarified how many subjects were excluded due to previously received periodontal treatment. More importantly, it was not mentioned whether the percentage of excluded subjects differed between the SS group and controls. When more subjects with previous periodontal treatment have been excluded in the SS group than in the control group, this will result in an underestimation of the number and severity of periodontal disease in SS patients. Therefore, as a result, exclusion of periodontal treated subjects could have introduced a risk of bias in the study population.

Conclusion

In the current study, no significant differences in the GI, PI, CAL, and PPD were observed in patients with SS compared to controls indicating that there is no evidence of a higher risk for periodontal disease in patients with SS. However, SS patients are more susceptible to caries compared to non-SS patients.

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