Primary Sjögren's Syndrome Impact on Smell, Taste, Sexuality and Quality of life in Female Patients: a systematic review and meta-analysis

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Received 05 Aug 2016, Accepted 04 Oct 2016, Accepted author version posted online: 20 Oct 2016, Published online: 14 Nov 2016

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Number of pages: 17
Number of figures: 2
Number of tables: 2

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Keywords: primary Sjögren's Syndrome, smell, sexual function, taste.

Abstract

Objectives: The aim of this study is to assess the impact of dryness caused by primary Sjögren's Syndrome (pSS) on smell, taste and sexual function in female patients, and its influence on quality of life.

Methods: Electronic databases including MEDLINE via Ovid, Web of Science, SCOUPUS, EMBASE and COCHRANE LIBRARY were searched until April 2016. Studies that assessed the function of smell, taste and sexuality in pSS patients, defined by the American European Consensus Group (AECG) criteria. Standardised mean differences (SMD) for individual studies using random-effects meta-analysis were feasible.

Results: Five studies incorporated 378 participants were included in the quantitative synthesis. The impact of pSS vs healthy controls was: smell SMD -0.78 (95% CI -1.29 to -0.27); taste SMD -1.01 (95% CI -1.54 to -0.49); total sexual function SMD -0.93 (95% CI -1.22 to -0.64); physical and mental component of the quality of life SMD -1.28 (95% CI -1.65 to -0.90) and SMD -0.83 (95% CI -1.27 to -0.40) respectively; anxiety and depression SMD 0.61 (95% CI 0.02, 1.20) and SMD 0.79 (95% CI 0.43 to 1.15) respectively.

Conclusion: pSS has a negative impact on smell, taste, sexual function and quality of life in women.

Introduction

Primary Sjögren's Syndrome (pSS) is a systemic autoimmune rheumatic disorder of unknown origin, affecting women nine times more commonly than men [1]. Inflammation of exocrine glands occurs as a result of excessive infiltration of autoantibodies leading to functional destruction. The burden of pSS is substantial and is compounded by the lack of effective treatment. Dryness of mucosal surfaces is the main characteristic feature of this syndrome, typically dry eyes and mouth. Yet, other mucosal surfaces can also be involved such as nasal and vaginal mucosa and can affect associated function and interfere with quality of life [2-4].

Smell and taste alteration are frequently reported symptoms by pSS patients. Studies have found that smell and taste are impaired and correlated with each other in pSS patients, and influenced by mucosal surfaces dryness [5, 6]. One study showed that taste disorders in Sjögren's patients are less frequently found than previously reported, and is linked to the reduction in salivary flow rate, in a way that impedes substances from reaching the taste buds [7]. Others, however, reported little association between taste deficit and mucosa dryness in Sjögren's patients [8, 9].

Women with pSS often suffer from vaginal dryness and dyspareunia with the possible explanation for these symptoms being local inflammation of the vaginal mucosa [4, 10-12]. An evidence was presented of the

association between oral symptoms and vaginal dryness in Sjögren's patients [11]. Other studies suggested that dryness and dyspareunia could adversely impact the sexual well-being of women with pSS [13, 14]. Sexual wellbeing is an important aspect of quality of life and addressing this is an essential component of delivering holistic patient-centred care. In this study, we aimed to determine the impact of mucosal dryness on smell, taste, sexual function and quality of life in women with pSS.

Methods

A prospective protocol was registered on a systematic review database (PROSPERO: CRD42015024354) [15]. This review was performed using recommended methods and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Search strategy and Eligibility criteria

Several electronic sources for published studies from inception to June 2015 were searched. The databases included Ovid-Medline, Web of Science, Scopus, Embase and Cochrane Library. MeSH and Boolean logic of the following search terms were used: Sjogren Syndrome, Sjogren Disease, hyposmia, anosmia, smell, smell*, olfact*, odour, nasal, nasal*, taste, taste*, gust, gust*, tastant, flavor, flavour, gustation, ageusia, hypogeusia, sex, sex*, obstet*, gyne*, gynae*, vagina, vagina*, dyspareunia. Recent issues of relevant publications and the reference lists of included texts and relevant review articles were searched. Experts were contacted for additional studies and data to clarify ambiguity. No search software has been used, EndNote was employed to merge retrieved citations and eliminate duplications. We placed no restriction on language or study population. Studies were selected for analysis if they satisfied the following criteria: i) Studies of pSS female patients vs. healthy controls; ii) Smell, taste and sexual dysfunction were a primary or secondary outcome; iii) Quality of life and mental health well-being were a secondary outcome iiii) Studies that used the American European Consensus Group (AECG) criteria as a standard to categorise SS patients [17]. Studies were eliminated if pSS diagnosis was based on clinical experience or other diagnostic criteria. Unpublished studies of the association has not been found. A flow chart of the study selection was generated.

Data extraction and quality assessment

All titles and abstracts for relevant studies were screened. Reasons for exclusion were documented (Supplementary-1). Full texts of eligible studies were independently read and data were extracted by two

reviewers (MA) and (NP). The two authors discussed the outcome with any disagreements resolved by consensus. The following data was extracted: study characteristics (authors, year of publication, title, country of the study, study design); population characteristics (inclusion and exclusion criteria, sample size, mean age, disease duration, response rate and drop out); intervention (type of intervention, mean score of questionnaires and/or clinical tests used, purpose of testing, outcome and summary of study). We modified the validated Newcastle-Ottawa Scale (NOS) instrument for quality assessment of the final selected studies. This modification was applied by including relevant items from NOS case-control, NOS cohort and the modified NOS cross-sectional designs as described by Herzog, Alvarez-Pasquin, Diaz, Del Barrio, Estrada and Gil [18] (Supplementary-2). Quality assessment was independently performed by MA and NP; any discrepancies were discussed and a third independent reviewer (KK) was involved if it could not be resolved. A star system was applied to evaluate primary study quality in terms of three criteria: Participant' selection, comparability, exposure and outcome assessment.

Meta-analysis

Standardised mean differences (SMD) and 95% confidence intervals (CIs) were calculated for continuous data. A random–effect model was applied to reduce statistical heterogeneity in combining data in order to get an overall SMD. Heterogeneity was evaluated via Chi^2 and I^2 at a *p*-value of ≤ 0.05. Overall effect was assessed using SMD with significance set at $p<0.05$. Funnel plot for the detection of publication bias and subgroup analysis to investigate heterogeneity will be applied when the number of trials is at least ten [19]. Where necessary authors were contacted by email for clarification or to obtain additional data. Statistical analysis was performed using Review Manager meta-analysis software (version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection

Final searches were undertaken in April 2016 and a total of 2767 articles were initially identified using the search strategy. After reviewing titles and/ or abstracts, no article studying the effect of dryness on the three elements together (smell, taste and sexuality) in Sjögren's patients was identified. Therefore, our search strategy was focused on studying the effect of pSS on each element separately and on the general quality of life and mental health wellbeing. Fifty three studies were deemed relevant and selected for full text assessment. Of these, five

articles fulfilled the criteria and were selected for qualitative and quantitative (meta-analysis) assessment (Figure 1).

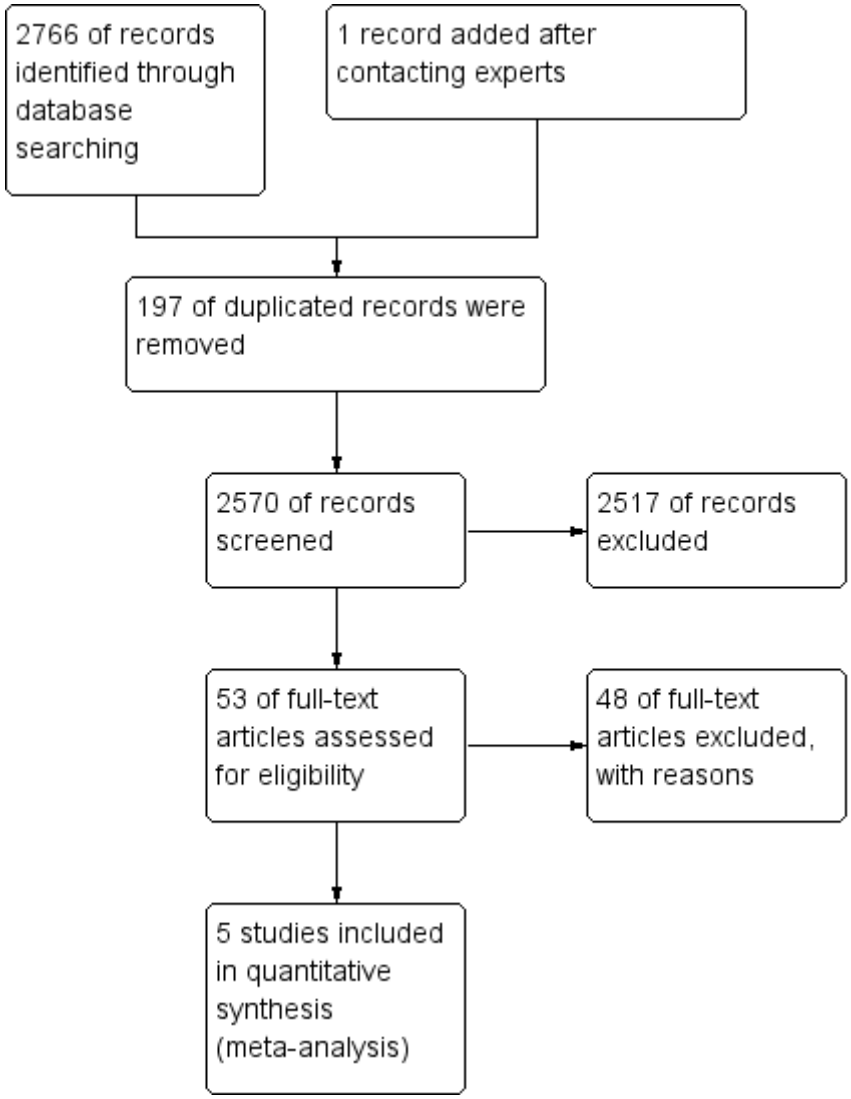


Figure-1 Studies selection process

Study characteristics

The characteristics of the five included studies for the current review are presented in Table 1. Primary study quality was adjudged as being moderate to high generally (Table-2). One study assessed the impact of pSS on smell and taste, with a total of 65 participants [6], and three studies evaluated the impact of pSS on sexuality, with a total of 201 participants [13, 14, 20]. Three studies [13, 14, 21] evaluated the impact of sexual dysfunction on mental health well-being by using the Hospital Anxiety and Depression Scale (HADS), and one study [20] assessed the impact of sexual dysfunction on mental health using Beck's Depression Inventory (BDI). Four studies [6, 13, 14, 21] measured the effect of pSS on Qol by using the Short Form-36 (SF-36), Short Form-12 (SF-12) and RAND 36-item Health Survey assessment tool, with a total of 314 participants. Bongi, Del Rosso, Orlandi and Matucci-Cerinic [21] assessed the sexual function using a different instrument modified from Hill's questionnaire with no data displayed; therefore, this study was not included in the meta-analysis.

Table-1 Characteristics of the five included studies

Reference	Country of publication	Study design as stated in the article	Screening	Participants in analysis	Mean age	Mean years of disease duration	Outcome	Summary of study
1. Kamel et al., 2009	UK, Wales	Prospective, Cross-Sectional study observational study	clinical sensory threshold tests & questionnaire	pSS = 28 Controls = 37	pSS =58 Controls = 56	4	Impairment of chemosensory function	Impairment of chemosensory perception & QoL in pSS patients compared with age and gender matched control
2. Bongi et al., 2013	Italy	Observational transversal study	Questionnaires	pSS = 62 Controls = 50	pSS = 62.82 Controls =61.66	6.45	Impaired sexual function in pSS	Impairment but no sig. dif. between pSS & controls in sexuality, mental health, fatigue & QoL
3. Ugurlu et al., 2014	Turkey	Cross sectional	Questionnaires	pSS = 32 Controls = 32	pSS =40.1 Controls = 37.4	NS	Impaired sexual function in pSS	Sexual dysfunction is affected by disease itself and depression. The disease itself is greater. Sexual dysfunction and depression is higher in pSS patients
4. Nimwegen et al., 2015	Netherland	Cross-sectional	Questionnaires	pSS = 46 Controls = 43	pSS =46.3 Controls = 44.4	7	Impaired sexual function & sexual distress	pSS patients experience significantly more sexual dysfunction and distress than controls. Sexual dysfunction is influenced by vaginal dryness, pain and fatigue as well as mental health disorders
5. Priori et al., 2015	Italy	Cross-sectional	Vaginal pH, pelvic exam, cervicovaginal swabs, Pap test (cases only) questionnaires(cases & controls)	pSS =24 Controls = 24	pSS = 50.4 Controls = 47	NS	Impaired sexual function in pSS	pSS patients have lower sexual functioning than healthy controls, high level of anxiety related with low level of quality of sexual life

Table-2 Quality assessment of the included studies measured by Modified Newcastle Ottawa Scale (M-NOS)

Studies	Selection						Comparability	Exposure			Outcome		Evidence quality
	Case definition	Representa-tiveness of cases	Selection of controls	Controls definition	Sample size	Outcome was not at start of study		Ascertain-ment of exposure	Same ascertainment for cases & controls	Non-respon se rate	Outcome assessment	Statistical analysis	
Kamel 2009	⋆	-	-	-	-	⋆	⋆⋆	⋆	⋆	-	⋆	⋆	High
Bongi 2013	⋆	-	-	⋆	⋆	⋆	⋆	-	-	-	⋆	⋆	Moderate
Ugurlu 2014	⋆	-	-	⋆	-	-	⋆⋆	-	⋆	-	⋆	⋆	Moderate
Nimwegen 2015	⋆	-	⋆	⋆	⋆	-	⋆⋆	-	⋆	-	⋆	⋆	High
Priori 2015	⋆	⋆	-	⋆	-	⋆	⋆⋆	-	⋆	⋆	⋆	⋆	High

0-4 poor; 5-7 moderate; 8-10 high; 11-13 very high

Smell and taste function

One study (Kamel et al., 2009), of moderate quality involving a total of 28 pSS patients and 37 healthy participants, compared the chemosensory function of smell and taste, and its impact on quality of life in pSS patients versus controls. The two senses had significantly deteriorated in pSS patients compared to age and gender matched controls, with about 50% of subjects suffering from hyposmia ($p = 0.002$) and 70% suffering from hypogeusia ($p < 0.001$). However, salivary flow rate measurement was not undertaken in a similar manner for all participants; therefore, the relationship between the impaired chemosensory perception and the degree of salivary glands dysfunction was not reported. In terms of the correlation between both senses, smell function was positively correlated with that of taste ($r = 0.35$, $p = 0.004$). The study also proved that age was inversely associated with smell thresholds ($r = -0.252$; $p = 0.04$), whilst no impact was found to be on taste dysfunction ($r = -0.15$, $p = 0.236$). Results of this study may not be applicable to the female population of Sjögren's patients as the sample consisted of 11% males in the pSS group. This study was the only one that met our inclusion criteria in terms of the assessment of smell and taste in Sjögren's patients; meta-analysis for these elements was therefore not possible.

Sexual function

Sexual function has been measured by FSFI in three included studies [13, 14, 20], and was compared between pSS patients (102 patients) and healthy controls (99 participants). A random-effects model was used in all domains, and the pooled results displayed significant difference between pSS patients and healthy controls. The SMD of the FSFI scores of pSS patients were lower than that of controls on each domain of sexual function: Desire ($P < 0.00001$, SMD -0.72, 95% CI -1.00 to -0.43), Arousal ($P < 0.00001$, SMD -0.93, 95% CI -1.22 to -0.64), lubrication ($P < 0.00001$, SMD -1.07, 95% CI -1.37 to -0.77), Orgasm ($P= 0.001$, SMD -0.60, 95% CI -0.96 to -0.23), Satisfaction ($P < 0.0001$, SMD -0.60, 95% CI -0.91 to -0.30), Pain ($P < 0.0001$, SMD -0.92, 95% CI -1.34 to -0.51), total FSFI ($P < 0.00001$, SMD -0.93, 95% CI -1.22 to -0.64).

Quality of Life

The quality of life of pSS patients has been assessed by SF-36, SF-12 and RAND-36 in four eligible studies [6, 13, 14, 21] and was compared between pSS patients (160 patients) and healthy controls (154 participants). A random-effect model was used in the meta-analysis of the Physical (PCS) and Mental Component Summary (MCS) due to statistical heterogeneity between studies ($P = 0.08$, $I^2 = 55\%$; $P = 0.02$, $I^2 = 70\%$ respectively). The pooled results combining scores from domains demonstrate lower quality of life in pSS group compared to

healthy controls on PCS and MCS (P < 0.00001, SMD -1.28, 95% CI -1.65 to -0.90; P = 0.0002, SMD -0.83, 95% CI -1.27 to -0.40 respectively).

Mental health well-being

Mental health well-being has been measured by HADS in four included studies [13, 14, 20, 21] and was compared between 132 pSS patients vs. 117 healthy controls in Anxiety (HADS-A), and 164 pSS patients vs. 149 healthy controls in Depression (HADS-D) respectively. A random-effect model was used in the meta-analysis due to statistical heterogeneity among studies (P= 0.004, I^2 = 82%; P = 0.07, I^2 = 57% respectively).

The pooled results of HADS-A and HADS-D showed that the SMD was significantly higher in pSS patients than in controls (P = 0.04, SMD 0.61, 95% CI 0.02 to1.20; P < 0.0001, SMD 0.79, 95% CI 0.43 to 1.15 respectively) (Table-3).

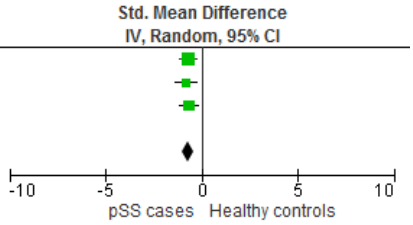
Publication bias and subgroup analysis

As the number of the included studies in each subgroup is less than ten, funnel plot assessments were not required.

A

Study or Subgroup	pSS patients Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	2.85	1.17	46	3.62	0.96	43	44.4%	-0.71 [-1.14, -0.28]
Priori et al., 2015	2.7	1.03	24	3.6	1.13	24	23.4%	-0.82 [-1.41, -0.23]
Ugurlu et al., 2014	2.8	1.1	32	3.6	1.3	32	32.2%	-0.66 [-1.16, -0.15]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.72 [-1.00, -0.43]**

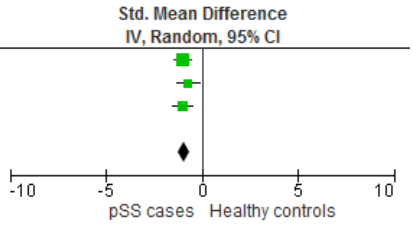
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 4.93 (P < 0.00001)



B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	3.3	1.91	46	4.9	1.16	43	43.8%	-1.00 [-1.44, -0.55]
Priori et al., 2015	3	1.4	24	4.1	1.63	24	25.0%	-0.71 [-1.30, -0.13]
Ugurlu et al., 2014	2.7	1.4	32	4	1.1	32	31.3%	-1.02 [-1.54, -0.50]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.93 [-1.22, -0.64]**

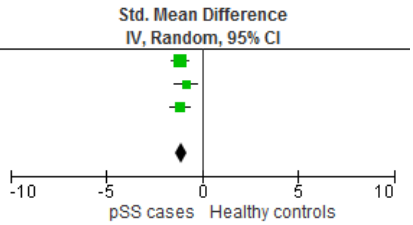
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 6.25 (P < 0.00001)



C

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	3.18	2.22	46	5.29	1.25	43	43.5%	-1.15 [-1.60, -0.70]
Priori et al., 2015	3.1	1.66	24	4.6	1.84	24	25.1%	-0.84 [-1.43, -0.25]
Ugurlu et al., 2014	3.3	1.7	32	5	1.2	32	31.3%	-1.14 [-1.67, -0.61]
Total (95% CI)			**102**			**99**	**100.0%**	**-1.07 [-1.37, -0.77]**

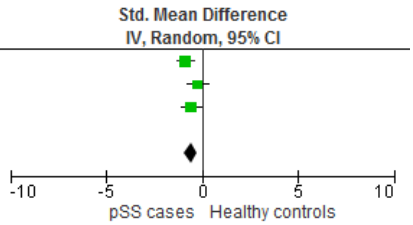
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 7.06 (P < 0.00001)



D

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	3.22	2.24	46	4.93	1.5	43	38.8%	-0.88 [-1.32, -0.45]
Priori et al., 2015	3.8	1.65	24	4.2	1.78	24	28.1%	-0.23 [-0.80, 0.34]
Ugurlu et al., 2014	2.5	1.3	32	3.2	1.1	32	33.1%	-0.57 [-1.07, -0.07]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.60 [-0.96, -0.23]**

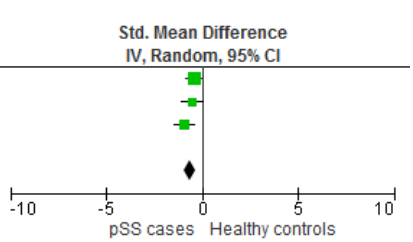
Heterogeneity: Tau² = 0.04; Chi² = 3.25, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 3.19 (P = 0.001)



E

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	3.95	1.75	46	4.65	1.53	43	44.1%	-0.42 [-0.84, -0.00]
Priori et al., 2015	4	1.63	24	4.9	1.66	24	25.2%	-0.54 [-1.11, 0.04]
Ugurlu et al., 2014	2.5	1.4	32	3.6	0.9	32	30.7%	-0.92 [-1.44, -0.41]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.60 [-0.91, -0.30]**

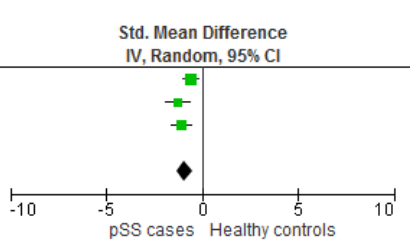
Heterogeneity: Tau² = 0.01; Chi² = 2.24, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 3.92 (P < 0.0001)



F

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	3.15	2.34	46	4.48	2.2	43	40.2%	-0.58 [-1.00, -0.16]
Priori et al., 2015	2.5	1.89	24	4.8	1.67	24	26.9%	-1.27 [-1.89, -0.64]
Ugurlu et al., 2014	2.5	1.4	32	3.8	1	32	32.9%	-1.06 [-1.58, -0.53]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.92 [-1.34, -0.51]**

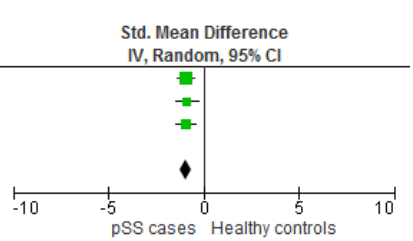
Heterogeneity: Tau² = 0.06; Chi² = 3.83, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 4.36 (P < 0.0001)



G

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nimwegen et al., 2015	19.65	10.34	46	27.87	6.07	43	44.1%	-0.95 [-1.39, -0.51]
Priori et al., 2015	19.1	7.33	24	26.1	8.79	24	24.2%	-0.85 [-1.44, -0.26]
Ugurlu et al., 2014	16.6	7.9	32	23.3	5.9	32	31.7%	-0.95 [-1.47, -0.43]
Total (95% CI)			**102**			**99**	**100.0%**	**-0.93 [-1.22, -0.64]**

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 6.22 (P < 0.00001)



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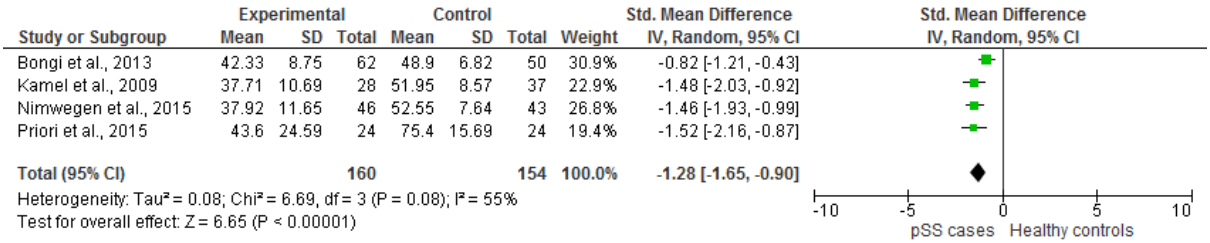

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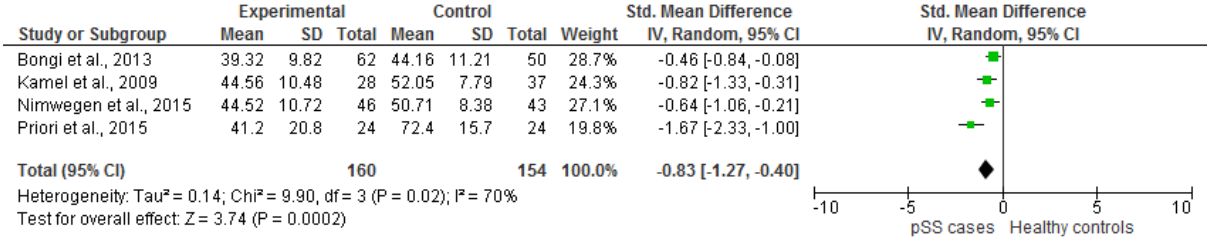

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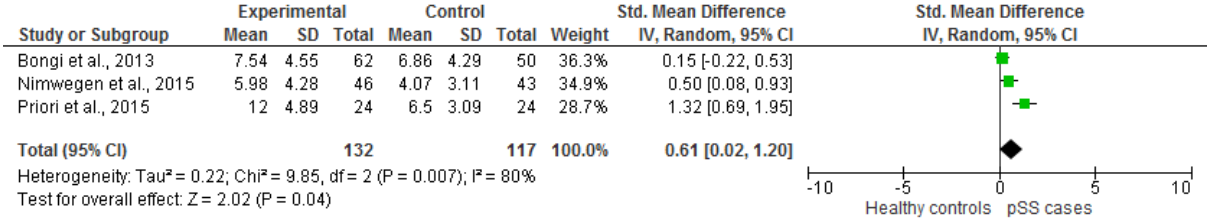

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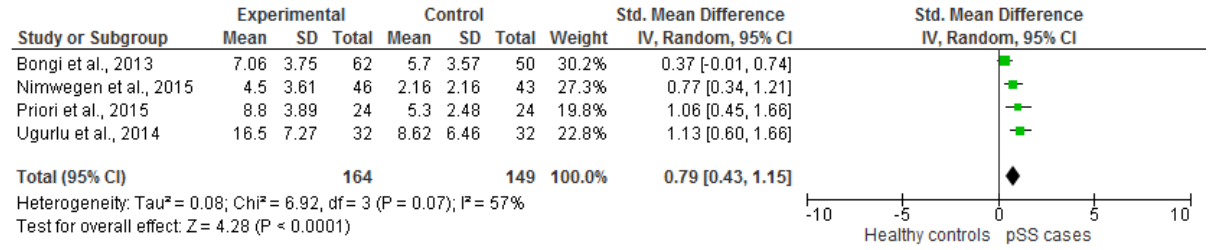

Figure-2 Forest plots of the sexual function A - G assessed by FSFI (A) Desire, (B) Arousal, (C) Lubrication, (D) Orgasm, (E) Satisfaction, (F) Pain, and (G) total FSFI. Quality of life (H and I) assessed by SF-12, SF-36 and RAND-36, (H) Physical component, (I) Mental component. Mental health well-being (J and K) assessed by HADS and BDI, (J) Anxiety (HADS-A), (K) Depression (HADS-D and BDI).

Discussion

The primary purpose of this review is to systematically assess the effect of mucosa dryness which is known to be part of pSS, on the senses that share this aspect, and whether a dysfunction exists, will be impacting the quality of life of patients. During our search, there was no one study in the literature assessing the impact of pSS on the smell and taste and sexuality collectively. Therefore, splitting the study's aim into three separate goals has been conducted.

Of the studies that met our inclusion criteria, Kamel et al [6] was the only study measured the effect of pSS on smell and taste and quality of life in pSS patients. The rest of eligible studies [13, 14, 20, 21] assessed the impact of sexual dysfunction on quality of life of pSS patients.

Our meta-analysis included five studies with a total number of 378 of participants (192 cases and 186 controls). The quality of included studies ranged between moderate [20, 21] and high [6, 13, 14]. We were unable to perform funnel plot or subgroup analysis owing to the limited number of studies available in each subgroup.

In terms of sexual function, three studies with a total of 201 participants (102 cases and 99 controls) were included [13, 14, 20]. No significant heterogeneity was identified on pain domain, whilst zero heterogeneity was observed on desire, arousal, lubrication, satisfaction and on the total FSFI. There was only one domain (orgasm) with significant heterogeneity between studies. Therefore, a random-effect model was applied. In the meta-analysis, a certain sexual dysfunction was found in pSS patients compared with healthy controls. The three analysed studies [13, 14, 20] came to agreement on the correlation between sexual activity and the low quality of mental health, where the latter may have a bidirectional effect on the sexual life. The studies also highlighted the impact of vaginal dryness on sexual dysfunction in pSS patients. In fact, there appear to be a suggestion in the literature that there are more than one element that influence sexual function in rheumatic patients, including joint pain, age and sex hormones [22, 23]. Two of the analysed studies [13, 14] found that sexual dysfunction does not correlate with the measurement assessed by physicians using the validated EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [18], but is associated more with the self-reported symptoms of the syndrome as rated by the EULAR Sjögren's Syndrome Patients' Reported Index (ESSPRI) [19]. However, there are no such correlations reported in the literature regarding the smell and taste.

In the quality of life meta-analysis, heterogeneity was observed in the four included studies and random-effect model was applied. The summarised scores of PCS and MCS demonstrated lower scores of physical and mental

components among individuals with pSS than in controls, which denotes to the adverse impact of the syndrome on patients' quality of life as a result of the sexual dysfunction. Yet, in this meta-analysis, quality of life has also been negatively impacted by the deficit of chemosensation that was assessed by Kamel et al, 2009. Therefore, we concluded that pSS has more than one aspect that impacts on quality of life. However, future studies are needed to determine which aspect is the most impacting patients' well-being.

Screening of the mental disorders, negative impact of pSS on mental health well-being was observed in the patients group compared to controls. Random-effect model was applied due to statistical heterogeneity. Three studies were included in the meta-analysis of anxiety where higher levels were shown in pSS group compared to controls. Four studies were included in the meta-analysis of depression, and was also found to be worse in patients compared to controls. Data were pooled at the suggested cut-off point of ≥8 [24, 25] therefore, we concluded that pSS has significantly increased anxiety and depression levels in pSS patients compared to controls.

The strength of the current review lies in its methodology that was conducted in accordance to PRISMA guidelines, to ensure high quality of studies selection and data extraction. Comprehensive literature search including all relevant electronic databases with no restriction on language, as well as manual search through references and journals were approached. Two reviewers worked independently with an overall agreement rate of 99%. Relying on a well-established diagnostic criteria of AECG in classifying pSS patients has enriched our inclusion criteria [17]. These criteria are valid, reliable and present a well-defined group of pSS by discriminating between primary and secondary SS. We had to follow restrictive inclusion criteria to reduce heterogeneity among studies that used different and unreliable diagnostic criteria to classify pSS patients.

Limitations of this study

The lack of primary research made it difficult to explore the potential cause of heterogeneity. However, two probable predictors for heterogeneity is the different age range across studies and the sample size, that is, larger studies demonstrate greater accuracy than smaller studies. Additional factors: the different quality of the included studies and selection bias in recruiting participants can also explain the resulted heterogeneity. Furthermore, it was not possible to adjust for potential confounders as we do not have access to studies data at individual level.

To the best of our knowledge, the present systematic review and meta-analysis is the first analysing the impact of pSS on the sexual function in Sjögren's patients. We concluded that pSS is adversely impacting patients' sexual life mood status. Future work is needed to look at whether psycho-sexual counselling can help women with pSS. Health professionals managing cases of pSS should consider enquiring about sexual complaints, since patients will not bring up the problem themselves. Research is needed concerning development of vaginal dryness treatment for pSS patients.

Conclusion

With this systematic review and meta-analysis we present evidence of the multidimensional impact of pSS on patients' well-being. Lack of primary research has been observed and therefore, further work and core outcome set is required to look at the effect of the syndrome on the senses of smell and taste and hence on quality of life.

Acknowledgements

The authors would like to thank **Jolien F. van Nimwegen** for her contribution to data collection.

Funding: This work is in partial fulfilment of a PhD degree, which is supported by the Iraqi Ministry of Higher Education and Scientific Research.

Disclosure statement: The authors declare no conflicts of interest.

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